MOLECULAR METABOLISM

Vascular effects of advanced glycation endproducts: Clinical effects and molecular mechanisms

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ABSTRACT

The enhanced generation and accumulation of advanced glycation endproducts (AGEs) have been linked to increased risk for macrovascular and microvascular complications associated with diabetes mellitus. AGEs result from the nonenzymatic reaction of reducing sugars with proteins, lipids, and nucleic acids, potentially altering their function by disrupting molecular conformation, promoting cross-linking, altering enzyme activity, reducing their clearance, and impairing receptor recognition. AGEs may also activate specific receptors, like the receptor for AGEs (RAGE), which is present on the surface of all cells relevant to atherosclerotic processes, triggering oxidative stress, inflammation and apoptosis. Understanding the pathogenic mechanisms of AGEs is paramount to develop strategies against diabetic and cardiovascular complications.

1. INTRODUCTION

Morbidity and mortality among people with diabetes mellitus are mostly triggered by premature cardiovascular disease (CVD) [1,2]. Elevated levels of circulating advanced glycation endproducts (AGEs) in the presence of hyperglycemia are believed to play a major role in the pathogenesis of macrovascular and microvascular disease observed in diabetes mellitus [3–6]. This review briefly describes the source of AGEs, their mechanisms of action and the specific effects on cells implicated in vascular homeostasis. Furthermore, key data from animal studies is presented along with the clinical evidence for their effects at the macrovascular and microvascular levels.

1.1. Literature research
A PubMed search was performed until September 2013 using the terms "advanced glycation endproducts" in combination with the terms "microvascular", "macrovascular", "endothelium", "retinopathy", "nephropathy", "neuropathy" or "cardiovascular".

2. DEFINITION AND SYNTHESIS OF AGEs

AGEs are a heterogeneous group of compounds formed by the nonenzymatic glycation of proteins, lipids or nucleic acids [7,8] within

the so-called "Maillard reaction", a tribute to the French scientist Louis Camille Maillard (1878–1936). This reaction consists of several steps (Figure 1). The first, reversible step takes place between the carbonyl group of a reducing sugar and an aminoterminal group of a protein, lipid or nucleic acid generating a so-called "Schiff base". By structural irreversible re-arrangements, more stable keto-amines are formed, called Amadori products (e.g. the $HbA1_c$) [9]. The Amadori products undergo further structural changes through oxidation, dehydration and degradation to finally yield highly stable AGEs compounds [9,10].

The carbonyl groups necessary for the reaction do not exclusively originate from carbohydrate metabolism, but can be also formed during lipid or protein degradation [11]. When the carbonyl group originates from the lipid catabolism (e.g. malondialdehyde), the products of the reaction are termed "advanced lipoxidation endproducts" (ALEs) [11]. However, the differentiation between AGEs and ALEs is not always possible: N^{ϵ}-carboxymethyllysine (CML), for example, can be formed during either carbohydrate or lipid catabolism and can therefore be attributed both terms AGE or ALE.

Usually the reaction leading to the formation of AGEs may take weeks to years and may affect especially long-lived substrates like collagen [12]. Under certain conditions, such as increased substrate availability (e.g. hyperglycemia), increased temperature and increased oxidative stress, the formation of AGEs can be reduced to several hours [13], also affecting short-lived substrates like hormones (e.g. insulin), enzymes,

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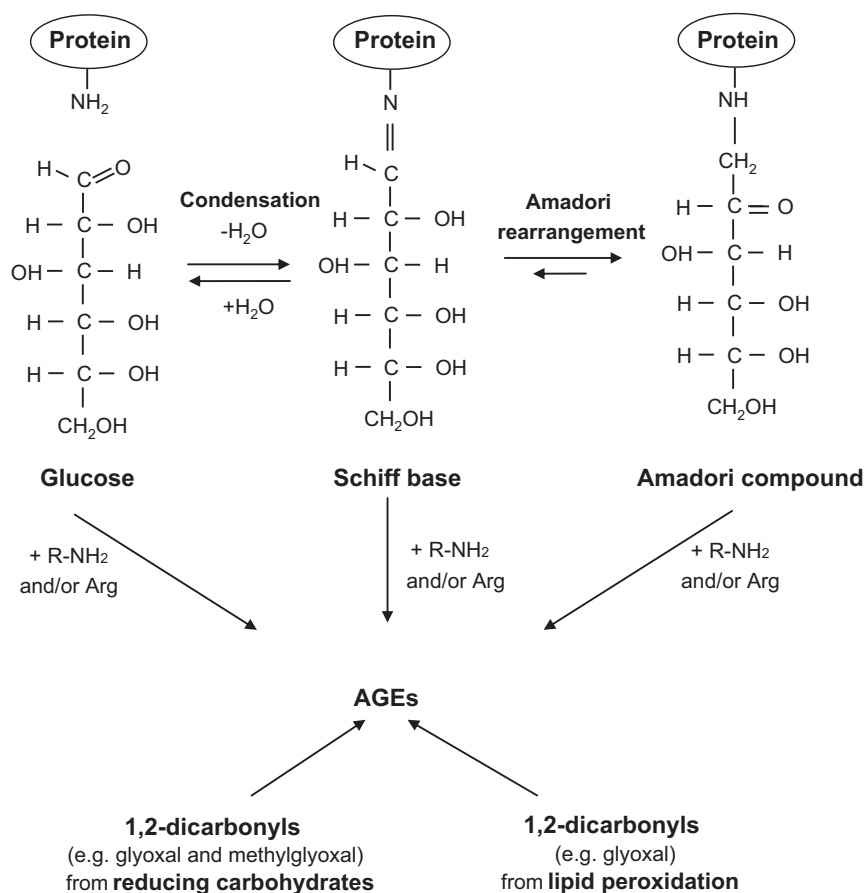
Figure 1: The synthesis of advanced glycation endproducts (AGEs) is a nonenzymatic reaction where in its classical form the reactive carbonyl group of a sugar reacts with the nucleophilic amino group of an amino acid (e.g. arginine=Arg) or a protein (R-NH₂). Adapted from Ahmed et al., Mol. Nutr. Food Res. 2005, 49:691–699 and T. Henle, Amino Acids 2005, 29:313–322.

amino acids or lipids and thus inducing functional and/or structural changes [14–18]. Highly reactive dicarbonyl compounds are generated during the conversion of Amadori products to AGEs, with methylglyoxal (MG) and 3-deoxyglucosone being the most studied AGE dicarbonyl precursors [19,20]. AGEs act either by modifying substrates, or by interacting with specific receptors; these mechanisms will be detailed in the course of this article.

Three main groups of AGEs have been described: (1) fluorescent cross-linking AGEs (e.g. pentosidine and crossline); (2) non-fluorescent cross-linking AGEs such as imidazolium dilysine cross-links resulting from reactions between glyoxal derivatives and lysine residues; (3) non-cross-linking AGEs (e.g. CML) [21–24].

3. SOURCES AND METABOLISM OF AGES

AGEs can be formed within the organism (endogenous source) or can originate from exogenous sources. Although AGEs are better known as by-products of hyperglycemia, they also form within food during heat-enhanced cooking [25]. Evidence has accumulated that dietary AGEs are partially absorbed [26,27] and either retained in the body or excreted in the urine [27–29]. These dietary AGEs represent an important source for circulating AGEs under in vivo conditions [30–32]. Moreover, smoking also serves as an additional exogenous source of AGEs [33].

The most important mechanisms involved in the degradation of endogenous AGEs are extracellular proteolysis as well as the AGEs-receptor (AGER1)-mediated intracellular uptake and degradation within cells like tissue macrophages (Figure 3) [8]. The degradation of AGEs by macrophages generates low-molecular, soluble peptides, also known as "second generation AGEs" that leave the cells, appear in blood and are finally excreted by the kidney depending on the kidney function [29,34]. In the liver, Kupffer cells and endothelial cells also seem to play an important role in the endocytosis and degradation of glycated substrates [35]. Under physiologic conditions, AGEs accumulate with age [36], but their accumulation seems to be exacerbated by some pathologic conditions: diabetes mellitus, renal failure, cardiovascular disease, Alzheimer's disease, rheumatoid arthritis, and others [3,10,31,37–39]. In these conditions, AGEs do not seem to be innocent bystanders, but rather contribute to pathophysiologic alterations.

4. METHODS FOR MEASURING AGES

Several methods are available for the measurement of AGEs. Circulating or tissue-bound AGEs can be measured by (i) enzyme-linked immunosorbent assays (ELISA) using monoclonal or polyclonal antibodies [30], (ii) fluorescence spectroscopy using the fluorescence properties of some AGEs [40], or (iii) high-performance liquid chromatography (HPLC) and mass spectrometry (MS), with the later method being probably the most reliable [10]. MS-based methods allow, for example, for measurements of the AGEs' representative CML in the urine by combining isotope dilution and gas chromatography (GC)–MS analysis. This method is sensitive, reproducible,

accurate, rather cheap and therefore often used in laboratories for the diagnosis and monitoring of age-related chronic diseases [10,41].

Ahmed et al. [42] have used liquid chromatography (LC) with triple quadrupole MS detection for the quantitative measurement of protein glycation, oxidation and nitration adducts. In patients suffering from uremia, LC has been combined with tandem mass spectrometric (LC–MS/MS) detection to accurately quantify glycation adducts in plasma, urine, and dialysate samples [43]. Finally, matrix-assisted laser desorption ionization-mass spectrometry with time-of-flight detection (MALDI-TOF/MS) seems to be a promising tool to analyze AGE-modified proteins [10,44].

Tissue-bound AGEs are usually measured in the skin because of its easy accessibility. The gold standard is represented by the biochemical analysis of skin biopsies [45], but rapid, non-invasive methods have also been applied to measure skin autofluorescence [40]. The measurement of skin autofluorescence was validated against biochemical analyses of AGEs in dermal tissue in biopsies taken from the same spot on the arm [40,46]. Subsequently, several studies have demonstrated that auto-fluorescence is elevated in people with diabetes [47] and in people with end-stage renal disease [48] when compared to control subjects.

Overall, the choice of the method depends on the purpose of the study. For example rapid, postprandial changes, or changes within short interventional studies, are usually assessed by measuring circulating AGEs rather than tissue-bound AGEs, while epidemiologic studies and long-term interventional studies focus on the measurement of tissue AGEs. For large screening studies, the measurement of skin autofluor-escence represents a tempting alternative [49].

5. MECHANISMS MEDIATING THE VASCULAR EFFECTS OF AGEs

Some of the mechanisms mediating the detrimental effects of AGEs on the vasculature are related to inflammation and oxidative stress [50], increased glycation of low-density and high-density lipoproteins (LDL, HDL) [51], activation of the pro-inflammatory inducible nitric oxide (NO)-synthase (iNOS) [52] and decreased NO availability [53]. Further mechanisms comprise the increased production of cytokines, e.g. insulin-like growth factor-1 (IGF-1) or the platelet derived growth factor (PDGF), which modify the migration of monocytes and macrophages as well as the proliferation of vascular smooth muscle cells (VSMC) [54,55]. The AGEs-induced effects can be classified according to their site of action or their receptor dependency.

AGEs-induced damage can occur to the vasculature, to the vascular cells and to the cells implicated in the vascular homeostasis via at least the following 4 mechanisms [56] (Figure 3):

(i) AGEs modify intracellular proteins, including those involved in the regulation of gene transcription [15].

(ii) Precursors of AGEs leave the cells via diffusion and modify nearby extracellular matrix molecules, subsequently altering the signaling between matrix and cells and ultimately causing cellular dysfunction [57].

(iii) AGEs and their precursors modify circulating proteins in the bloodstream, thereby altering their function.

(iv) Circulating proteins modified by AGEs bind to and activate AGEs receptors, thereby altering the production of inflammatory cytokines and growth factors, which in turn drive cellular and tissue damage [30,54]. Indeed, the activation of certain receptors for AGEs (e.g. RAGE) promotes inflammatory response, mainly by the activation of nuclear factor κB (NFκB), apoptosis, prothrom-botic activity, expression of adhesion molecules, and oxidative stress [58–60] (Figure 2). Furthermore, the AGE–RAGE interaction can activate the inducible nitric oxide synthase (iNOS). The iNOS resides mainly in inflammatory cells,

is regulated by inflammatory cytokines and can be stimulated by oxidative stress in an NFκB-dependent manner, resulting in toxic concentrations of nitric oxide (NO) [52,61]. The latter reacts with oxygen radicals, forming a highly reactive metabolite, peroxynitrite, which interacts with proteins and DNA, causing nitration of proteins (nitrative stress), DNA damage, further activation of NFκB, caspase-3, and vascular cell apoptosis [62,63].

The deleterious effects of AGEs on the vasculature can also be classified as either receptor-dependent or receptor-independent.

5.1. Receptor-independent effects of AGEs

Glycation of proteins and lipoproteins can alter their normal function by several mechanisms: change in molecular conformation, alteration in enzyme activity, changes in clearance and interference with receptor recognition [64]. It has been demonstrated that glycation of LDL particles on the apolipoprotein B (ApoB) and phospholipid components [65,66] contributes to the exacerbation of atherosclerosis. Higher levels of glycated LDL (AGE-LDL) were found in patients with diabetes and suggested to belong to the features of dyslipidemia related to diabetes mellitus and renal insuffi-ciency [66,67]. Glycation of ApoB results in impairment of LDL receptor-mediated uptake with subsequently reduced clearance of LDL [68]. In contrast, AGE-LDL uptake by macrophages is greater than that of native LDL by an LDL-receptor-independent mechanism involving a high-capacity, low-affinity scavenger receptor [69]. Glycation thus enhances LDL uptake by human aortic intimal cells [70] and monocyte-derived macrophages [69], thereby stimulating the formation of foam cells and promoting atherosclerosis [64]. Alternatively, glycation of LDL promotes atherosclerosis via the increased susceptibility of AGE-LDL for oxidation, another critical pathway in the development of atherosclerosis [64,68,71]. A large body of evidence links 'post-translational' modifications such as glycation and oxidation of plasma lipoproteins to vascular mechanisms implicated in the pathogenesis of diabetic retinopathy. Under physiolo-gical conditions, the inner and outer blood–retina barriers prevent the extravasation of plasma components [72,73]. Enhanced leakage is present even before and further increases with the manifestation of diabetic retinopathy in proportion with disease severity [72]. Several studies reported large amounts of modified LDL in the retina of persons with diabetes and its toxicity for retinal capillary pericytes [72], endothelial cells [74] and Muller cells [75]. Heavily-oxidized glycated LDL and HDL can impair retinal pigment epithelial cells by inducing a generation of reactive oxygen species (ROS), endoplasmic reticulum (ER) stress, autophagy, apoptosis and decreasing glutathione peroxidase 1 (GPX-1) [73]. GPX-1 is considered the most important cytosolic and mitochondrial antioxidant enzyme in humans, detoxifying hydrogen peroxide and lipid peroxides [76]. On the other hand, glycation and oxidation of HDL decrease its antioxidant properties of suppressing the enhanced ROS generation induced by oxidized and glycated LDL, thereby further reducing the cellular antioxidant capacity. ER stress induces protein misfolding and triggers the "unfolded protein response" [77], which is implicated in the death of retinal neurons and vascular cells in patients with diabetes [78]. The ER is sensitive to oxidative stress induced by oxidized LDL as well as heavily oxidized glycated LDL [73,79] and prolonged ER stress induces ultimately apoptosis via activation of the pro-apoptotic transcription factor C/EBP-homologous protein (CHOP). Indeed, heavily oxidized glycated LDL markedly enhances CHOP expression in retinal pigment epithelial cells [73].

Autophagy plays a major role in intracellular homeostasis by removing damaged organelles, cell membranes and proteins, as well as preser-ving nutrients [80]. However, prolonged ER stress may switch autophagy from a protective role to one promoting cell death. Autophagy was
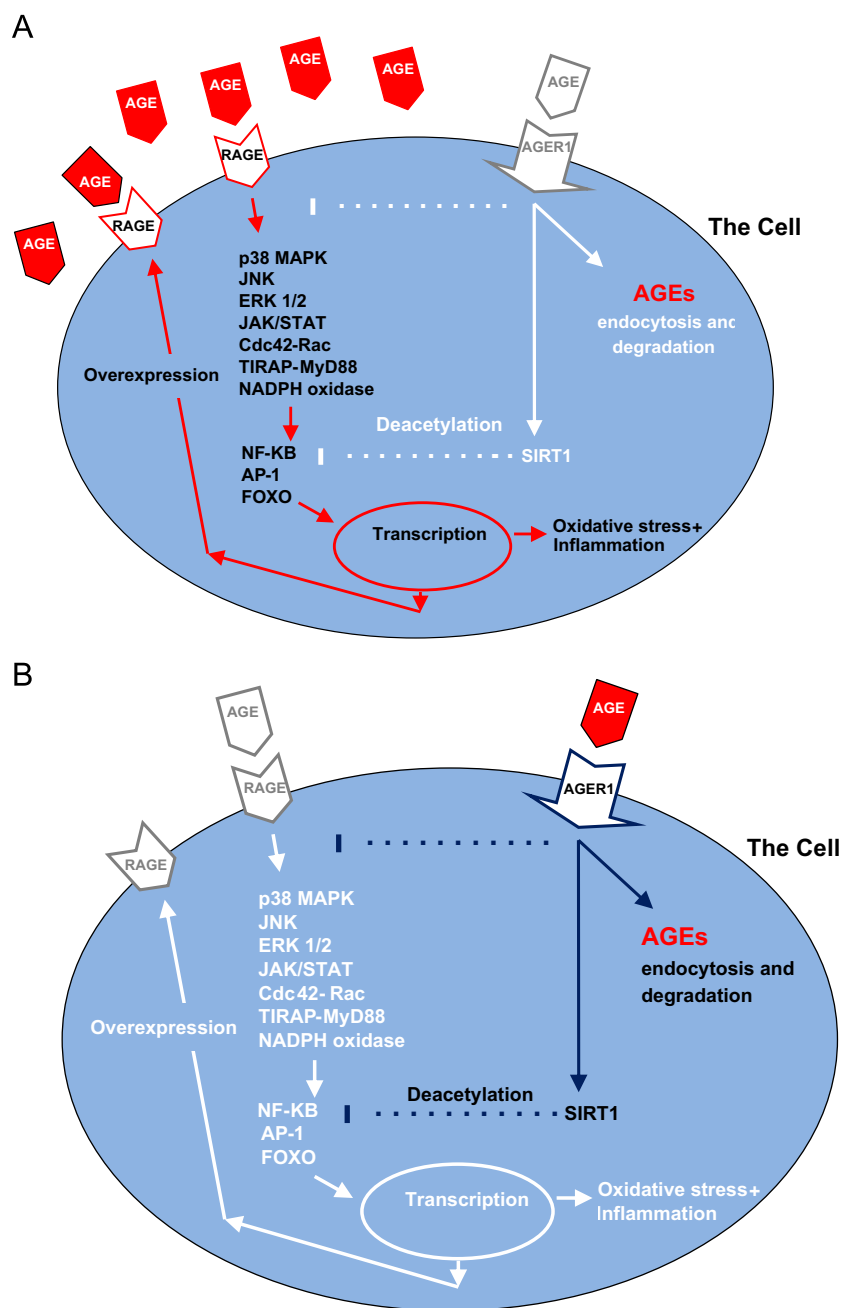
Figure 2: Receptor-dependent pathways activated by AGEs. A substrate excess of AGEs leads to a RAGE overexpression and exacerbation of RAGE-dependent pathways (a), while a low AGEs substrate availability activates mainly AGER1-triggered signals, AGEs endocytosis and degradation (b). Adapted from Poulsen et al., Food and Chemical Toxicology, 2013.

shown to mediate the deleterious effects of heavily oxidized glycated LDL on Muller cells, retinal pigment epithelial cells and retinal pericytes [73,75,79]. Taken together, oxidation and glycation of LDL seems to potentiate its pathogenic role, while oxidized glycated HDL partly loses its protective role.

Last but not the least, glycation of matrix proteins – collagen VI, laminin and vitronectin – increases the turnover of heparane sulfate, which in turn stimulates the compensatory overproduction of other matrix components [81]. Modification of matrix proteins by glycation also affects the interaction of transmembrane integrin receptors with some matrix ligands, altering stability. For example, the modification of the cell-binding domains of type VI collagen decreases endothelial cell adhesion [64,81].

5.2. Receptor-dependent effects of AGEs

AGE receptors are present on the surface of different cell types: macrophages, adipocytes, endothelial cells, and vascular smooth muscle cells (VSMC) [7,59,82–85]. Several types of receptors including scavenger receptors (macrophage scavenger receptor-AI, macrophage scavenger receptor-AII, CD68, and CD36), RAGE, AGE-R1, AGE-R2, and AGE-R3 have been described [86,87]. Although scavenger receptors are responsible for the removal of AGEs, RAGE likely mediates most biological effects of AGEs [88]. RAGE is a member of the immunoglobulin multiligand receptor family, which is involved in intracellular signal transduction. Its activation promotes inflammatory responses, apoptosis, prothrombotic activity, expression of adhesion molecules, and oxidative stress [59,60,89].
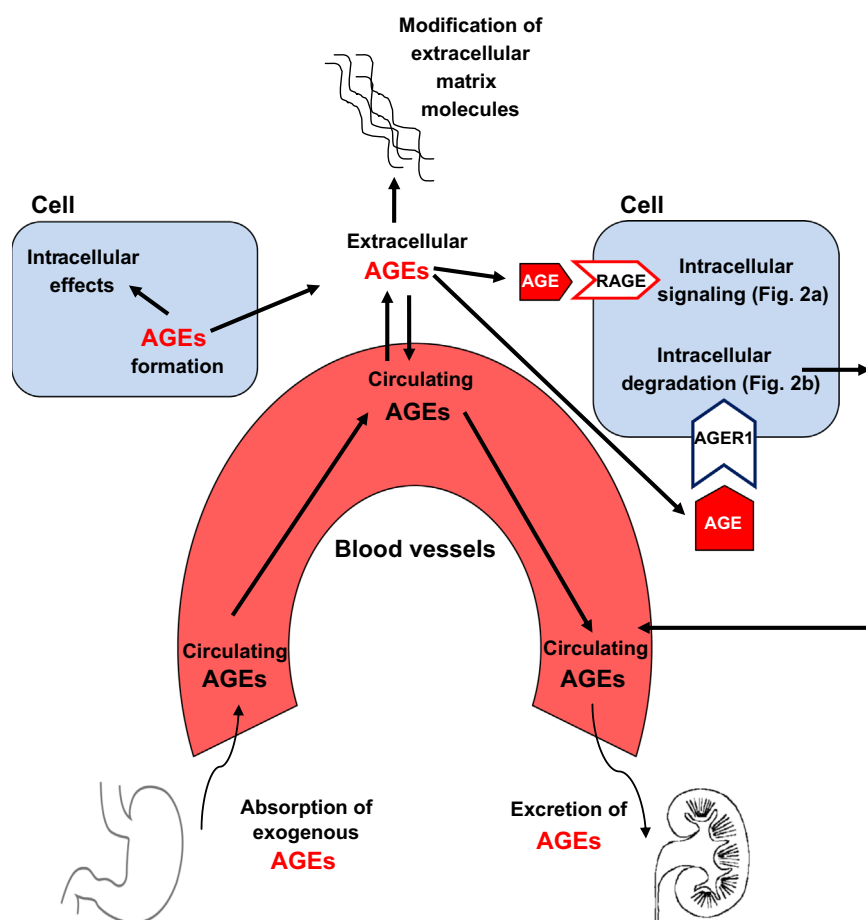
Figure 3: The cycle of endogenous and exogenous AGEs.

The interaction between AGEs and RAGE activates several intracellular signaling cascades, for example the family of mitogen-activated protein (MAP) kinase, members of the JAK-STAT signaling family, CDC42, RAC1 and other members of the Ras family, SRC1, members of the SMAD signaling family and phosphoinositide 3-kinase [59,89–91]. Moreover, RAGE signaling activates the central transcription factors [89], nuclear factor (NF)-ƘB [59], cAMP-response-element-binding protein (CREB)-1 [92], early growth response (EGR)-1 [93] and activator protein (AP)-1 [94] (Figure 1). Recent articles provide insights into the factors influencing AGEs–RAGE binding, as well as into RAGE structure, highlighting the importance of receptor oligomerization for the formation of active signaling complexes [95–98]. However, the precise mode of oligomerization remains unclear in the context of various ligands. Several of the RAGE ligands share structural features such as alpha and beta sheets, suggesting that RAGE recognizes three-dimensional structures [88,99]. The detailed mechanisms and consequences of RAGE activation are discussed in detail in recent comprehensive reviews [6,59,89,100,101]. Here we focus on its relevance for cardiovascular disease. Briefly, RAGE is up-regulated in atheromatous lesions [102] and in diabetes [103], suggesting that AGEs-mediated pathomechanisms are exacerbated in these diseases [104].

Which AGEs or which of their precursors bind to RAGE is still a matter of debate. N(ε)-carboxy-methyl-lysine (CML), N(ε)-carboxy-ethyl-lysine (CEL) and methylglyoxal have been suggested to bind to RAGE [98,105–107], but others have questioned whether AGEs containing CML modifications [108] or early glycation adducts (fructosyllysine peptides) [98] can activate RAGE. Taking into consideration the multitude of existing AGEs, further

studies are warranted to clarify which AGEs or AGEs classes bind to RAGE and which do not.

Of note, RAGE does not exclusively bind AGEs, but also non-AGEs substrates like some members of the S100/calgranulin family of pro-inflammatory and migration-stimulating molecules [89,109]. Recently, Poulsen et al. [110] discussed the relevance of the in vivo interaction between AGEs and RAGE by highlighting that the interaction between AGEs (mainly CML) and RAGE does not uniformly induce an inflammatory response [108,111–113]. This could be due to the existence of splice variants of RAGE on certain cells [112], the fact that not all AGEs interact with RAGE [108] or the presence of endotoxin in some preparations of AGEs [111,113]. There are two further aspects that might mitigate the importance of AGEs–RAGE interaction in vivo. The AGEs–RAGE interaction seems to depend on the molecular size of the AGEs compounds. In addition, the affinity of AGEs for RAGE might be lower in vivo as compared to in vitro studies [110]. Indeed, comparing the affinity of low-molecular-weight (free or < 30 kDa) and high-molecular-weight CML binding to RAGE revealed that only the high-molecular weight CML interacts with RAGE [98,106,114].

Since only low-molecular weight AGEs are absorbed from the gut, one can hypothesize that diets enriched in AGEs will give rise only to low-molecular weight AGEs in the circulation with scarce AGEs–RAGE interaction. In contrast, Birlouez-Aragon et al. [115] showed that AGEs-rich diets increase circulating high-molecular-weight AGEs, suggesting that dietary AGEs can induce the endogenous formation of larger AGEs capable of RAGE activation. In line, Vlassara et al. [30] provide

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evidence that diets with a high AGEs content given for several weeks induce an inflammatory response, typical for the AGEs–RAGE interaction. Nevertheless, RAGE seems to have more complex roles than we believe at the moment, since mice lacking RAGE show increased bone mass and bone mineral density and decreased bone resorption in vivo, suggesting a role of RAGE in osteoclast maturation and function [116]. Moreover, RAGE-dependent responses might aim at rapidly responding to vascular injuries and facilitate repair under physiological conditions, but set in motion a vicious circle of injury as soon as exacerbated AGEs concentrations occur [100].

6. EFFECTS OF AGES IN CELLS CONTRIBUTING TO ABNORMAL VASCULAR FUNCTION

Studies in animal models and in vitro have shown that AGEs impact the function of different cell types implicated in atherosclerosis: endothelial cells [54,63,117], platelets [118], monocytes/macrophages [119] or vascular smooth muscle cells [120], thus explaining their association with vascular disease [121].

6.1. Effects of AGEs on endothelial cells, pericytes and angiogenesis

AGEs' interaction with RAGE-expressing endothelial cells results in reduced endothelial barrier function with increased permeability and subendothelial lipid entry. The AGEs–RAGE interaction triggers the expression of adhesion molecules, e.g. VCAM-1 [122], and promotes transendothelial migration of monocytes, thereby contributing to the formation of foam cells [122–124].

Xu et al. [53] demonstrated that the incubation of human umbilical vein endothelial cells (HUVEC) with AGEs-modified albumin, but not with a high-glucose medium, exerted a concentration- and time-dependent suppression of the endothelial isoform of the NO-synthase (NOS). NOS suppression was biphasic with a rapid component due to suppression of its serine phosphorylation and a slower component involving decreased NOS expression.

Many endothelial cell processes are dependent upon intracellular Ca^{2+} and Ca^{2+}-signaling, among them the synthesis of NO from arginine by the enzyme NOS. A study by Naser et al. [125] showed in bovine aortic endothelial cells that incubation with AGEs for 5 minutes causes an acute intracellular store depletion of Ca^{2+}, such that the Ca^{2+} signal stimulated by the subsequent application of other agents acting upon that store was reduced. The same authors suggested as one of the mechanisms the generation of ROS from NAD(P)H oxidase.

Impaired angiogenesis of the peripheral vasculature contributes to delayed wound healing, exacerbated peripheral limb ischemia, and exacerbates cardiac morbidity via reduction of collateral vessel development [126]. Peppa et al. showed in genetically diabetic mice that dietary AGEs from a high-AGEs (H-AGEs) diet exert adverse effects on wound healing compared to a low-AGEs (L-AGEs) diet [127]. Wounds of L-AGEs-treated mice exhibited lower skin AGEs deposits, increased epithelialization, angiogenesis, inflammation, granulation tissue deposition, and enhanced collagen organization compared with H-AGEs mice. Interestingly, the modality of wound healing seemed to be influenced by food AGEs with re-epithelialization being the dominant mode of wound closure in H-AGEs-fed mice compared with wound contraction that prevailed in L-AGEs-fed mice.

The mechanisms of impaired angiogenesis induced by AGEs were partly explained by Liu et al. [107], who demonstrated in vitro using endothelial cells and mouse aortas that methylglyoxal (the highly reactive AGEs precursor) reduces endothelial angiogenesis through RAGE-mediated,

peroxynitrite-dependent and autophagy-induced vascular endothelial growth factor receptor 2 (VEGFR2) degradation. VEGFR2 represents the principal receptor for vascular endothelial growth factor signaling, which leads to vasodilatation, endothelial cell migration and proliferation [107,128,129].

Apoptosis of retinal capillary pericytes and endothelial cells is one of the pathomechanisms contributing to the progression of diabetic retinopathy [130]. Nagaraj et al. [131] have shown in retinas from alloxan-induced diabetic dogs, intense AGEs-specific modifications of the basement membrane proteins of retinal capillaries. Considering at the mechanisms using in vitro cultured bovine retinal capillary pericytes and HUVECs incubated with MG, the authors found an apoptosis of retinal pericytes induced by MG that was increased by 55% compared to pericytes incubated on a fibronectin media without MG. The authors proposed that the enhanced apoptosis occurred through the p38MAPK-mediated oxidative pathway and was accompanied by marked actin degradation and a dramatic decrease in αB-crystallin, a small heat shock protein present mainly in the eye lens. While this study suggested that pericytes' apoptosis occurs because of the surrounding basement membrane protein modification by AGEs, other studies suggested that pericytes apoptosis is due to the effects of circulating AGEs, resulting in VEGF overproduction [132] and binding to surface AGEs-receptors [133].

6.2. Effects of AGEs on platelets

Platelets activated by different agonists (ADP, collagen and thrombin) express P-selectin (CD62), an adhesion molecule on the surfaces of activated endothelial cells and activated platelets, and adhere to endothelial cells and blood leukocytes as a key event in the sequence of thrombus formation, inflammatory reaction [134] and in the development of atherosclerotic lesions and atherothrombosis [135].

AGEs strongly activate platelets obtained from both healthy humans and patients with type 2 diabetes [118]. AGEs stimulated the expression of CD62 up to 7.1-fold and CD63, a cell surface glycoprotein forming complexes with integrins and a potential blood platelet activation marker, up to 2.2-fold at the platelet surface membrane in a concentration- and time-dependent manner. Given the postprandial increase in circulating AGEs [136,137], this might explain the postprandial frequency of acute ischemic events. In this study, platelet activation by AGEs was accompanied by an increase in platelet RAGE expression without proof of an AGEs–RAGE interaction.

Platelets contain specific storage granules, which fuse with the plasma membrane during degranulation. This mechanism can possibly lead to the translocation of RAGE to the platelet surface. However, additional studies are required to examine the AGEs interaction with RAGE or other receptors for AGEs on a platelet surface. Of note, Zhu et al. [138] demonstrated an interaction between AGEs and CD36 on platelet surfaces resulting in a prothrombotic phenotype.

6.3. Effects of AGEs on inflammatory cells

Binding of AGEs to RAGE on the surface of monocytes induces the production of mediators: interleukin-1, tumor necrosis factor-α, platelet-derived growth factor and insulin-like growth factor-1, resulting in chemotaxis and inflammatory response [119,139–141].

Kirstein et al. [119] showed that (i) in vitro- and in vivo-formed AGEs are chemotactic for human blood monocytes, (ii) sub-endothelial AGEs can selectively induce monocyte migration across an intact endothelial cell monolayer, and (iii) subsequent monocyte interaction with AGEs-containing matrix results in the expression of platelet-derived growth factor. These authors highlighted that their findings support the hypothesis that AGEs can act as signals for the normal turnover of

senescent tissue protein by means of the AGEs-specific receptor system.

Also, AGEs increase the expression of blood-borne tissue factor (TF) by cultured or fresh isolated monocytes as shown in different studies [142,143]. Bierhaus and colleagues found that the induction of TF expression by cultured endothelial cells with AGEs is mediated via the AGEs–RAGE interaction [144]. High expression of TF on monocytes and vascular endothelium appears to regulate the inflammatory response [145,146]. Adherence of activated platelets to leukocytes is a key event in the sequence of thrombus formation, and platelet recruitment by activated leukocytes plays an important role in modulating an inflammatory reaction [134]. Hu and co-workers have shown that diabetic individuals show elevated circulating platelet-leukocyte aggregates in blood [147]. Gawlowski et al. demonstrated that glycated albumin and MG induce Mac-1 expression on neutrophils, which results in enhanced formation of platelet–leukocyte aggregates [143].

Zhang and coworkers [148] found in pigs with streptozotocin-induced diabetes that diabetes increased NAD(P)H oxidase activity and oxidative stress, producing inflammatory responses in porcine coronary media and adventitia. They examined the underlying mechanisms in isolated coronary fibroblasts and demonstrated that AGEs, rather than glucose itself, upregulate the expression of interleukin-6, VCAM-1, and monocyte chemotactic protein-1 mRNAs. These changes were paralleled by increased interleukin-6 secretion and augmented leukocyte adhesion to AGE-stimulated coronary cells. Furthermore, AGEs increased the expression of phosphorylated forms of mitogen-activated protein kinases in coronary cells (ERK1/2 and JNK) and resulted in redox-sensitive expression of inflammatory genes. These effects were inhibited by several inhibitors of oxidative pathways [NAD(P)H oxidase inhibitors, N-acetylcysteine, and pyrrolidine dithiocarbamate].

Wang et al. [149] studied cultured macrophages, A7r5 aortic smooth muscle cells, in vitro as well as an animal model of arteriosclerosis and diabetes. Streptozotocin (STZ)-diabetic male apoE($-/-$) mice were fed a semi-synthetic high-fat diet (HFD) plus daily injections of CML (10 mg/kg/day). The STZ-CML-HFD condition resulted in early atherosclerotic plaques at 2 months and typical advanced plaques at 4 months. Deposition of CML and expression of RAGE in the aortic wall were mainly restricted to the atherosclerotic plaques. Both animal and cell studies consistently demonstrated that the CML/RAGE axis may first initiate apoptosis of macrophages in atherosclerotic lesions and then induce bone morphogenetic protein 2 (BMP-2)-core-binding factor α1 (cbfα1) and alkaline phosphatase (ALP)-calcification dependent cascade in a high-lipid, apoptosis-coexisting environment. From these data, the authors suggested that the CML–RAGE interaction plays an important role in atherosclerotic calcification in diabetes, through the induction of macrophages' apoptosis, followed by the osteogenic differentiation of aortic smooth muscle cells.

6.4. Effects of AGEs on vascular smooth muscle cells (VSMC)

There is also evidence that the activation of RAGE on VSMC promotes cellular proliferation by mechanisms likely mediated by cytokine or growth factors [64,150]. Neointima formation in response to arterial injury involves VSMC proliferation and migration, potentially leading to arterial stenosis, thrombosis and ischemia in atherosclerosis, hypertension and arterial revascularization. RAGE activation by glycated albumin induced in cultured VSMC increased proliferation and migration by suppressing adenosine monophosphate kinase (AMPK) activation [120]. Some further mechanisms linking RAGE activation to VSMC proliferation might be represented by extracellular signal-regulated kinase (ERK) activation [151–153], autophagy induction [152], the activation of signal

transducer and activator of transcription (STAT)3/oncoprotein provirus integration site for Moloney murine leukemia virus (Pim1)/nuclear factor of activated T-cells (NFAT) axis [154], and activation of the serine/threonine kinase Akt1 [155]. Furthermore, activation of RAGE induces osteogenic differentiation of VSMC and thereby promotes vascular calcification through Notch/Msx2 induction [156].

Finally, accumulation of the membrane attack complex of complement (MAC) in blood vessels promotes proliferation of fibroblasts and VSMC [157]. While the regulatory membrane protein CD59 normally restricts MAC accumulation, its glycation results in MAC inactivation, as well as in the atherosclerosis-promoting proliferation of fibroblasts and VSMC [158].

7. VASCULAR EFFECTS OF AGES IN ANIMAL MODELS

The detection of AGEs and overexpressed receptors for AGEs in atheromatous plaques and lesions, as well as within lipid accumulations in VSMC and macrophages from diabetic patients, has narrowed the path between AGEs and atherosclerosis [102,159–161].

In genetically hypercholesterolemic apolipoprotein E-deficient (apoE ($-/-$)), streptozotocin-induced diabetic mice, a diet with a low AGEs content compared to an isocaloric standard diet with a high AGEs content resulted in $>50\%$ smaller lesions at the aortic root after 2 months. Only serum AGEs differed by about 53%, while no differences were noted in plasma glucose, triglycerides, or cholesterol levels between both groups [162].

Insulin resistance and reduced levels of HDL are prominent risk factors for cardiovascular disease and dietary AGEs were shown to increase circulating insulin levels and decrease circulating HDL levels in the db/db mouse model [163].

In another mouse model of genetic hypercholesterolemia, Lin et al. [164] showed that lowering of dietary AGEs reduces neointimal formation after arterial injury and suggested that dietary restriction of AGEs may have a potential role in the prevention of restenosis after angioplasty.

Vlassara et al. [165] administered AGE-modified albumin to nondiabetic rats and rabbits, alone or in combination with the AGE-crosslink inhibitor aminoguanidine. AGEs treatment for 2–4 weeks led to a sixfold higher content of AGEs content in aortic tissue samples compared to untreated controls, which was accompanied by increased vascular permeability and markedly impaired vasodilatatory responses to acetylcholine and nitroglycerin. These effects were significantly reduced by treatment with aminoguanidine. Moreover, mononuclear cell migratory activity was enhanced in subendothelial and periarteriolar regions of various tissues from AGEs-treated rats when compared to tissues from animals treated with aminoguanidine. The authors concluded that AGEs can induce complex vascular alterations resembling those seen in diabetes or aging, independent of metabolic or genetic factors, and that these changes can be reversed by the AGE-crosslink inhibitor aminoguanidine.

In rats, aminoguanidine administration was also effective in preventing diabetes-induced formation of fluorescent advanced nonenzymatic glycosylation products and cross-linking of arterial wall connective tissue protein in vivo [166]. Furthermore, aminoguanidine treatment for 18 months prevented increases in the AGEs content in aged cardiac, aortic, and renal tissues, markedly inhibited age-related albuminuria and proteinuria as well as age-related cardiac hypertrophy and preserved endothelium-dependent and endothelium-independent vascular function in non-diabetic female Sprague-Dawley and Fischer 344 rats [167].

Soluble RAGE (sRAGE, composed of the extracellular ligand-binding domain of RAGE), binds AGEs and blocks their interaction with RAGE,

thus partly reducing the detrimental effects of AGEs (Figure 2). A series of studies demonstrated that treatment with sRAGE for approximately 6 weeks resulted in dose-dependent reduction of the atherosclerotic lesion area and complexity, together with a decrease in AGEs, vascular inflammation and oxidative stress in apoE-null mice, while plasma glucose, cholesterol and triglyceride concentrations remained similar to vehicle treated mice [168,169]. In another study, administration of sRAGE stabilized already existing atherosclerotic lesions [170]. Finally, Wendt et al. [171] bred apo E−/− mice into the db/db background and treated them with sRAGE. These animals had significantly reduced atherosclerotic lesion area independent of the prevailing glycemia and lipidemia, thereby highlighting an important role of AGEs–RAGE interaction in mediating proatherogenic mechanisms.

These studies showed that higher circulating concentrations of AGEs, particularly food-derived AGEs, can induce cross-linking of arterial wall connective tissue protein [166], aortic atherosclerotic lesions [162], neointimal formation after arterial injury [164], increase vascular permeability and markedly impair vascular vasodilatatory response [165]. On the other hand, inhibitors of AGEs such as aminoguanidine or soluble RAGE can counteract diabetes- or age-induced effects of AGEs on the vasculature, suggesting that dietary or therapeutic interventions can be effective – at least in animal models – in preventing some key pro-atherosclerotic mechanisms.

8. VASCULAR EFFECTS OF AGES IN CLINICAL STUDIES

Studies in animal and cellular models have provided evidence for the implication of AGEs in vascular disease and explained some of the underlying mechanisms. In humans, several clinical studies have linked AGEs to cardiovascular disease, particularly in patient with diabetes mellitus. Kiuchi and coworkers [172] reported higher serum AGEs concentrations in type 2 diabetes patients with coronary artery disease (CAD) than in patients without obstructive CAD and higher than in normoglycemic patients with and without obstructive CAD. Similar results were reported by Kilhovd et al. [173] and Aso et al. [174]. Moreover, serum AGEs were found to be associated with the degree of CAD in patients with type 2 diabetes and obstructive CAD. Of note, elevation of serum AGEs in patients undergoing percutaneous coronary intervention was identified as an independent risk factor for restenosis in diabetes mellitus [175].

Prospective studies also support the association of AGEs with cardio-vascular disease (CVD). In type 1 diabetes, circulating AGEs were associated in a 12-years follow-up study with incident fatal and nonfatal CVD as well as all-cause mortality [3].

In female, but not in male type 2 diabetes patients, elevated serum AGEs predicted mortality due to CAD during a follow-up of more than 18 years [176]. These authors reported a similar gender-specific pattern, in that serum levels of AGEs predicted both total and CAD-induced mortality in normoglycemic women [177].

Studying patients with chronic heart failure (CHF) with only 9% also having diabetes, Hartog et al. [178] demonstrated that CML predicted a composite outcome (death, heart transplantation, ischemic cardiovascular events and hospitalization due to heart failure) even after adjustment for age, gender, etiology of heart failure and several other known predictors of CHF outcome.

The above-mentioned studies linked high AGEs concentrations to cardiac disease and its outcome. But these studies could not prove a causal relationship, so that the question remained unsolved whether AGEs are innocent bystanders or contribute to the development of cardiovascular disease. We demonstrated that changing the cooking method alone (and thereby changing the amount of ingested AGEs), has a relevant transient impact on postprandial microvascular and macro-vascular endothelial function in persons with type 2 diabetes mellitus [137]. On the other hand, we recently reported that acute oral administration of AGEs alone transiently impairs endothelial function as an early marker of atherosclerosis [179–181], supporting the concept that nutritional AGEs can have a direct detrimental effect on vasculature in humans [182].

Noninvasive measurements have shown that skin autofluorescence (SAF) is increased in people with increased cardiovascular risk such as people with carotid artery stenosis and peripheral artery disease, independent of the presence of diabetes [183]. An association of SAF with the one-year incidence of major adverse cardiac events has also been reported [184]. SAF provides also additional information on the UK Prospective Diabetes Study (UKPDS) risk score for the estimation of cardiovascular prognosis in people with type 2 diabetes mellitus [185].

9. POTENTIAL THERAPEUTIC OPPORTUNITIES TARGETING AGE-RELATED PROCESSES

In line with our data [137], several studies found that restriction of dietary AGEs was accompanied by a fall in circulating AGEs and a decrease in markers of oxidative stress, inflammation, endothelial dysfunction and insulin resistance in patients with diabetes mellitus [30,186], renal failure [31] as well as in healthy persons [115]. Since changing the cooking method (e.g. reducing temperature, increasing humidity, decreasing the pH) is highly effective in influencing the amount of AGEs contained in food [25], this might represent a simple, meaningful and cost-effective intervention against the AGEs burden.

Thiamine and its prodrug benfotiamine activate the enzyme transketolase, thus activating the pentose-5-phosphate glycolytic path and blocking other pathways involved in the development of diabetes complications, among them the production of AGEs [187]. Clinical and experimental studies have strengthened these findings [136,188,189] but endpoint studies are still awaited.

Besides thiamiane, sRAGE and aminoguanidine, many other substances were attributed roles against AGEs: drugs specifically developed as AGEs inhibitors (pyridoxamine, hydrazono-oxo-thiazolidine, 2,3-diaminophenazine), AGEs breakers (N-phenacylthiazolium, pyridoxamine), anti-inflammatory drugs with anti-glycation properties (e.g. tenilsetam, diclofenac, aspirin), renoprotective drugs with AGEs inhibition activity (angiotensin-converting enzyme-inhibitors, angiotensin-II receptor blockers, hydralazine), metabolically active drugs and vitamins with anti-AGEs properties (pyridoxamine, metformin, aldose reductase inhibitors), antioxidants and free radical trapping agents (carnosine, flavonoid-rich herbal extracts, curcumin), and AGEs inhibitors with chelating properties (carnosine, pyridoxamine, temocaprilat, tenilsetam, cerivastatin, pioglitazone, acarbose, etc.) [190,191]. However, many of these substances need validation by clinical studies.

10. CONCLUSIONS

Increases in AGEs can result from increased endogenous production under conditions of hyperglycemia or from exogenous dietary sources. AGEs exert their deleterious effects on the vasculature by both receptor-dependent and receptor-independent mechanisms. The receptor for AGEs, RAGE, seems to mediate most of the biological effects of AGEs by generating ROS and stimulating inflammatory pathways. In diabetic

states, AGEs production is increased and RAGE is up-regulated, whereas the AGEs scavenger receptor is down-regulated, possibly resulting in lower AGEs clearance. Thus, it is conceivable that diabetes triggers AGEs-mediated mechanisms, which could contribute to the increased cardiovascular morbidity and other diabetes-related complications. Nevertheless, in vivo evidence describing the importance of the clearance of AGEs by scavenger receptors compared to other potential pathways in removing AGEs is still lacking. Importantly, the signaling pathways believed to mediate AGEs–RAGE effects are only shown at very early time points of AGEs–RAGE interaction. However these early time points are not important for long-term effects, which is a typical feature of RAGE signaling. Of note, RAGE may also play a role in bone homeostasis as well as in vascular regeneration following injuries.

The relevance of the many forms of AGEs and their precursors has been addressed only recently. For example, Bierhaus and coworkers provided evidence that methylglyoxal plays an important role in the development of diabetes-related hyperalgesia [192]. AGEs also modify the function of different cells implicated in atherosclerosis, thereby reducing the activity of NOS and intracellular Ca^{2+}-dependent signaling by endothelial cells, activating platelets, increasing chemotaxis and inflammation mediated by monocytes/macrophages or promoting cellular proliferation and osteogenic differentiation of VSMC.

The results of the DCCT-EDIC study have strengthened the role of the so-called "glycemic memory", postulating that metabolic control over several years predicts the development of diabetic complications [193]. The fact that glycated proteins form under hyperglycemic conditions and chronically accumulate within organs that are prone to diabetes-related complications suggests AGEs as ideal candidates mediating the "glycemic memory" [150,194,195]. On the one hand, inhibitors of AGEs (aminoguanidine, thiamine, benfotiamine, pyridoxamine or soluble RAGE) can counteract diabetes- or age-induced effects of AGEs on vasculature in preclinical studies. On the other hand, several studies have shown that dietary restriction of AGEs is feasible in patients with diabetes or renal failure as well as in healthy persons and results in marked decrease in circulating AGEs and markers of oxidative stress, inflammation, endothelial dysfunction and insulin resistance.

Taken together, there is compelling evidence for a detrimental role of AGEs in driving vascular disease. Nevertheless, better understanding of the underlying mechanisms will be paramount for the development of treatment strategies targeting AGEs and thereby aiming at improving morbidity and mortality in persons with diabetes mellitus.

CONFLICT OF INTEREST

Authors have no conflict of interest to disclose related to the topic of this article.

REFERENCES

[1] Seshasai, S.R., Kaptoge, S., Thompson, A., Di, A.E., Gao, P., Sarwar, N., Whincup, P.H., Mukamal, K.J., Gillum, R.F., Holme, I., Njolstad, I., Fletcher, A., Nilsson, P., Lewington, S., Collins, R., Gudnason, V., Thompson, S.G., Sattar, N., Selvin, E., Hu, F.B., Danesh, J., 2011. Diabetes mellitus, fasting glucose, and risk of cause-specific death. New England Journal of Medicine 364:829–841.

[2] Hobbs, F.D., 2006. Type-2 diabetes mellitus related cardiovascular risk: new options for interventions to reduce risk and treatment goals. Atherosclerosis Supplements 7:29–32.

[3] Nin, J.W., Jorsal, A., Ferreira, I., Schalkwijk, C.G., Prins, M.H., Parving, H.H., Tarnow, L., Rossing, P., Stehouwer, C.D., 2011. Higher plasma levels of advanced glycation end products are associated with incident cardiovascular disease and all-cause mortality in type 1 diabetes: a 12-year follow-up study. Diabetes Care 34:442–447.

[4] Brownlee, M., 2001. Biochemistry and molecular cell biology of diabetic complications. Nature 414:813–820.

[5] Tan, K.C., Chow, W.S., Ai, V.H., Metz, C., Bucala, R., Lam, K.S., 2002. Advanced glycation end products and endothelial dysfunction in type 2 diabetes. Diabetes Care 25:1055–1059.

[6] Ramasamy, R., Yan, S.F., Schmidt, A.M., 2012. The diverse ligand repertoire of the receptor for advanced glycation endproducts and pathways to the complications of diabetes. Vascular Pharmacology 57:160–167.

[7] Vlassara, H., 1997. Recent progress in advanced glycation end products and diabetic complications. Diabetes 46 (Suppl. 2):S19–S25.

[8] Vlassara, H., Palace, M.R., 2003. Glycoxidation: the menace of diabetes and aging. Mount Sinai Journal of Medicine 70:232–241.

[9] Ahmed, N., 2005. Advanced glycation endproducts–role in pathology of diabetic complications. Diabetes Research and Clinical Practice 67:3–21.

[10] Mendez, J.D., Xie, J., Aguilar-Hernandez, M., Mendez-Valenzuela, V., 2010. Trends in advanced glycation end products research in diabetes mellitus and its complications. Molecular and Cellular Biochemistry 341:33–41.

[11] Miyata, T., Kurokawa, K., van Ypersele de, S.C., 2000. Advanced glycation and lipoxidation end products: role of reactive carbonyl compounds generated during carbohydrate and lipid metabolism. Journal of the American Society of Nephrology 11:1744–1752.

[12] Monnier, V.M., Bautista, O., Kenny, D., Sell, D.R., Fogarty, J., Dahms, W., Cleary, P.A., Lachin, J., Genuth, S., 1999. Skin collagen glycation, glycoxidation, and crosslinking are lower in subjects with long-term intensive versus conventional therapy of type 1 diabetes: relevance of glycated collagen products versus HbA1c as markers of diabetic complications. DCCT skin collagen ancillary study group. Diabetes control and complications trial. Diabetes 48:870–880.

[13] Schiekofer, S., Andrassy, M., Chen, J., Rudofsky, G., Schneider, J., Wendt, T., Stefan, N., Humpert, P., Fritsche, A., Stumvoll, M., Schleicher, E., Haring, H.U., Nawroth, P.P., Bierhaus, A., 2003. Acute hyperglycemia causes intracellular formation of CML and activation of ras, p42/44 MAPK, and nuclear factor kappaB in PBMCs. Diabetes 52:621–633.

[14] Vlassara, H., Bucala, R., 1996. Recent progress in advanced glycation and diabetic vascular disease: role of advanced glycation end product receptors. Diabetes 45 (Suppl. 3):S65–S66.

[15] Giardino, I., Edelstein, D., Brownlee, M., 1994. Nonenzymatic glycosylation in vitro and in bovine endothelial cells alters basic fibroblast growth factor activity. A model for intracellular glycosylation in diabetes. Journal of Clinical Investigation 94:110–117.

[16] Hunter, S.J., Boyd, A.C., O'Harte, F.P., McKillop, A.M., Wiggam, M.I., Mooney, M.H., McCluskey, J.T., Lindsay, J.R., Ennis, C.N., Gamble, R., Sheridan, B., Barnett, C.R., McNulty, H., Bell, P.M., Flatt, P.R., 2003. Demonstration of glycated insulin in human diabetic plasma and decreased biological activity assessed by euglycemic-hyperinsulinemic clamp technique in humans. Diabetes 52:492–498.

[17] Howard, M.J., Smales, C.M., 2005. NMR analysis of synthetic human serum albumin alpha-helix 28 identifies structural distortion upon amadori modification. Journal of Biological Chemistry 280:22582–22589.

[18] Yeboah, F.K., Alli, I., Yaylayan, V.A., Yasuo, K., Chowdhury, S.F., Purisima, E.O., 2004. Effect of limited solid-state glycation on the conformation of lysozyme by ESI-MSMS peptide mapping and molecular modeling. Bioconjugate Chemistry 15:27–34.

[19] Baynes, J.W., Thorpe, S.R., 1999. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. Diabetes 48:1–9.

[20] Thornalley, P.J., Langborg, A., Minhas, H.S., 1999. Formation of glyoxal, methylglyoxal and 3-deoxyglucosone in the glycation of proteins by glucose. Biochemical Journal 344 (Pt. 1):109–116.

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[21] Hegab, Z., Gibbons, S., Neyses, L., Mamas, M.A., 2012. Role of advanced glycation end products in cardiovascular disease. World Journal of Cardiology 4:90–102.

[22] Taneda, S., Monnier, V.M., 1994. ELISA of pentosidine, an advanced glycation end product, in biological specimens. Clinical Chemistry 40:1766–1773.

[23] Hartog, J.W., Voors, A.A., Bakker, S.J., Smit, A.J., Van Veldhuisen, D.J., 2007. Advanced glycation end-products (AGEs) and heart failure: pathophysiology and clinical implications. European Journal of Heart Failure 9:1146–1155.

[24] Onorato, J.M., Thorpe, S.R., Baynes, J.W., 1998. Immunohistochemical and ELISA assays for biomarkers of oxidative stress in aging and disease. Annals of the New York Academy of Sciences 854:277–290.

[25] Uribarri, J., Woodruff, S., Goodman, S., Cai, W., Chen, X., Pyzik, R., Yong, A., Striker, G.E., Vlassara, H., 2010. Advanced glycation end products in foods and a practical guide to their reduction in the diet. Journal of the American Dietetic Association 110:911–916.

[26] Forster, A., Kuhne, Y., Henle, T., 2005. Studies on absorption and elimination of dietary maillard reaction products. Annals of the New York Academy of Sciences 1043:474–481.

[27] Foerster, A., Henle, T., 2003. Glycation in food and metabolic transit of dietary AGEs (advanced glycation end-products): studies on the urinary excretion of pyrraline. Biochemical Society Transactions 31:1383–1385.

[28] Erbersdobler, H.F., Faist, V., 2001. Metabolic transit of Amadori products. Nahrung 45:177–181.

[29] Koschinsky, T., He, C.J., Mitsuhashi, T., Bucala, R., Liu, C., Buenting, C., Heitmann, K., Vlassara, H., 1997. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. Proceedings of the National Academy of Sciences of the United States of America 94:6474–6479.

[30] Vlassara, H., Cai, W., Crandall, J., Goldberg, T., Oberstein, R., Dardaine, V., Peppa, M., Rayfield, E.J., 2002. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proceedings of the National Academy of Sciences of the United States of America 99:15596–15601.

[31] Uribarri, J., Peppa, M., Cai, W., Goldberg, T., Lu, M., He, C., Vlassara, H., 2003. Restriction of dietary glycotoxins reduces excessive advanced glycation end products in renal failure patients. Journal of the American Society of Nephrology 14:728–731.

[32] Uribarri, J., Peppa, M., Cai, W., Goldberg, T., Lu, M., Baliga, S., Vassalotti, J.A., Vlassara, H., 2003. Dietary glycotoxins correlate with circulating advanced glycation end product levels in renal failure patients. American Journal of Kidney Diseases 42:532–538.

[33] Cerami, C., Founds, H., Nicholl, I., Mitsuhashi, T., Giordano, D., Vanpatten, S., Lee, A., Al-Abed, Y., Vlassara, H., Bucala, R., Cerami, A., 1997. Tobacco smoke is a source of toxic reactive glycation products. Proceedings of the National Academy of Sciences of the United States of America 94:13915–13920.

[34] Turk, N., Mornar, A., Mrzljak, V., Turk, Z., 2004. Urinary excretion of advanced glycation endproducts in patients with type 2 diabetes and various stages of proteinuria. Diabetes and Metabolism 30:187–192.

[35] Smedsrod, B., Melkko, J., Araki, N., Sano, H., Horiuchi, S., 1997. Advanced glycation end products are eliminated by scavenger-receptor-mediated endocytosis in hepatic sinusoidal Kupffer and endothelial cells. Biochemical Journal 322 (Pt. 2):567–573.

[36] Semba, R.D., Nicklett, E.J., Ferrucci, L., 2010. Does accumulation of advanced glycation end products contribute to the aging phenotype? Journals of Gerontology Series A: Biological Sciences and Medical Sciences 65:963–975.

[37] Ahmed, N., Thornalley, P.J., 2007. Advanced glycation endproducts: what is their relevance to diabetic complications? Diabetes, Obesity and Metabolism 9:233–245.

[38] Munch, G., Schinzel, R., Loske, C., Wong, A., Durany, N., Li, J.J., Vlassara, H., Smith, M.A., Perry, G., Riederer, P., 1998. Alzheimer's disease–synergistic effects of glucose deficit, oxidative stress and advanced glycation endproducts. Journal of Neural Transmission 105:439–461.

[39] de, G.L., Hinkema, H., Westra, J., Smit, A.J., Kallenberg, C.G., Bijl, M., Posthumus, M.D., 2011. Advanced glycation endproducts are increased in rheumatoid arthritis patients with controlled disease. Arthritis Research and Therapy 13:R205.

[40] Meerwaldt, R., Graaff, R., Oomen, P.H., Links, T.P., Jager, J.J., Alderson, N.L., Thorpe, S.R., Baynes, J.W., Gans, R.O., Smit, A.J., 2004. Simple non-invasive assessment of advanced glycation endproduct accumulation. Diabetologia 47:1324–1330.

[41] Petrovic, R., Futas, J., Chandoga, J., Jakus, V., 2005. Rapid and simple method for determination of Nepsilon-(carboxymethyl)lysine and Nepsilon-(carboxyethyl) lysine in urine using gas chromatography/mass spectrometry. Biomedical Chromatography 19:649–654.

[42] Ahmed, N., Babaei-Jadidi, R., Howell, S.K., Beisswenger, P.J., Thornalley, P.J., 2005. Degradation products of proteins damaged by glycation, oxidation and nitration in clinical type 1 diabetes. Diabetologia 48:1590–1603.

[43] Thornalley, P.J., 2005. Measurement of protein glycation, glycated peptides, and glycation free adducts. Peritoneal Dialysis International 25:522–533.

[44] Kislinger, T., Humeny, A., Peich, C.C., Becker, C.M., Pischetsrieder, M., 2005. Analysis of protein glycation products by MALDI-TOF/MS. Annals of the New York Academy of Sciences 1043:249–259.

[45] Genuth, S., Sun, W., Cleary, P., Sell, D.R., Dahms, W., Malone, J., Sivitz, W., Monnier, V.M., 2005. Glycation and carboxymethyllysine levels in skin collagen predict the risk of future 10-year progression of diabetic retinopathy and nephropathy in the diabetes control and complications trial and epidemiology of diabetes interventions and complications participants with type 1 diabetes. Diabetes 54:3103–3111.

[46] Smit, A.J., Gerrits, E.G., 2010. Skin autofluorescence as a measure of advanced glycation endproduct deposition: a novel risk marker in chronic kidney disease. Current Opinion in Nephrology and Hypertension 19:527–533.

[47] Lutgers, H.L., Graaff, R., Links, T.P., Ubink-Veltmaat, L.J., Bilo, H.J., Gans, R.O., Smit, A.J., 2006. Skin autofluorescence as a noninvasive marker of vascular damage in patients with type 2 diabetes. Diabetes Care 29:2654–2659.

[48] McIntyre, N.J., Chesterton, L.J., John, S.G., Jefferies, H.J., Burton, J.O., Taal, M.W., Fluck, R.J., McIntyre, C.W., 2010. Tissue-advanced glycation end product concentration in dialysis patients. Clinical Journal of the American Society of Nephrology 5:51–55.

[49] Meerwaldt, R., Links, T.P., Graaff, R., Hoogenberg, K., Lefrandt, J.D., Baynes, J.W., Gans, R.O., Smit, A.J., 2005. Increased accumulation of skin advanced glycation end-products precedes and correlates with clinical manifestation of diabetic neuropathy. Diabetologia 48:1637–1644.

[50] Cai, W., Gao, Q.D., Zhu, L., Peppa, M., He, C., Vlassara, H., 2002. Oxidative stress-inducing carbonyl compounds from common foods: novel mediators of cellular dysfunction. Molecular Medicine 8:337–346.

[51] Duell, P.B., Oram, J.F., Bierman, E.L., 1991. Nonenzymatic glycosylation of HDL and impaired HDL-receptor-mediated cholesterol efflux. Diabetes 40:377–384.

[52] Wever, R.M., Luscher, T.F., Cosentino, F., Rabelink, T.J., 1998. Atherosclerosis and the two faces of endothelial nitric oxide synthase. Circulation 97:108–112.

[53] Xu, B., Ji, Y., Yao, K., Cao, Y.X., Ferro, A., 2005. Inhibition of human endothelial cell nitric oxide synthesis by advanced glycation end-products but not glucose: relevance to diabetes. Clinical Science (London) 109:439–446.

[54] Vlassara, H., 1996. Advanced glycation end-products and atherosclerosis. Annals of Medicine 28:419–426.

[55] Stirban, A., 2010. The role of AGEs and ROS in atherosclerosis. Herz 35:170–180.

[56] Stirban, A., Rosen, P., Tschoepe, D., 2008. Complications of type 1 diabetes: new molecular findings. Mount Sinai Journal of Medicine 75:328–351.

[57] Charonis, A.S., Reger, L.A., Dege, J.E., Kouzi-Koliakos, K., Furcht, L.T., Wohlhueter, R.M., Tsilibary, E.C., 1990. Laminin alterations after in vitro nonenzymatic glycosylation. Diabetes 39:807–814.

[58] Rosen, P., Nawroth, P.P., King, G., Moller, W., Tritschler, H.J., Packer, L., 2001. The role of oxidative stress in the onset and progression of diabetes and its complications: a summary of a Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. Diabetes/Metabolism Research and Reviews 17:189–212.

[59] Bierhaus, A., Humpert, P.M., Morcos, M., Wendt, T., Chavakis, T., Arnold, B., Stern, D.M., Nawroth, P.P., 2005. Understanding RAGE, the receptor for advanced glycation end products. Journal of Molecular Medicine 83:876–886.

[60] Ramasamy, R., Vannucci, S.J., Yan, S.S., Herold, K., Yan, S.F., Schmidt, A.M., 2005. Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. Glycobiology 15:16R–28R.

[61] Griscavage, J.M., Wilk, S., Ignarro, L.J., 1996. Inhibitors of the proteasome pathway interfere with induction of nitric oxide synthase in macrophages by blocking activation of transcription factor NF-kappa B. Proceedings of the National Academy of Sciences of the United States of America 93:3308–3312.

[62] Mohamed, A.K., Bierhaus, A., Schiekofer, S., Tritschler, H., Ziegler, R., Nawroth, P.P., 1999. The role of oxidative stress and NF-kappaB activation in late diabetic complications. Biofactors 10:157–167.

[63] Kowluru, R.A., 2005. Effect of advanced glycation end products on accelerated apoptosis of retinal capillary cells under in vitro conditions. Life Sciences 76:1051–1060.

[64] Aronson, D., Rayfield, E.J., 2002. How hyperglycemia promotes atherosclerosis: molecular mechanisms. Cardiovascular Diabetology 1:1.

[65] Bucala, R., Mitchell, R., Arnold, K., Innerarity, T., Vlassara, H., Cerami, A., 1995. Identification of the major site of apolipoprotein B modification by advanced glycosylation end products blocking uptake by the low density lipoprotein receptor. Journal of Biological Chemistry 270:10828–10832.

[66] Bucala, R., Makita, Z., Koschinsky, T., Cerami, A., Vlassara, H., 1993. Lipid advanced glycosylation: pathway for lipid oxidation in vivo. Proceedings of the National Academy of Sciences of the United States of America 90:6434–6438.

[67] Bucala, R., Makita, Z., Vega, G., Grundy, S., Koschinsky, T., Cerami, A., Vlassara, H., 1994. Modification of low density lipoprotein by advanced glycation end products contributes to the dyslipidemia of diabetes and renal insufficiency. Proceedings of the National Academy of Sciences of the United States of America 91:9441–9445.

[68] Steinbrecher, U.P., Witztum, J.L., 1984. Glucosylation of low-density lipoproteins to an extent comparable to that seen in diabetes slows their catabolism. Diabetes 33:130–134.

[69] Klein, R.L., Laimins, M., Lopes-Virella, M.F., 1995. Isolation, characterization, and metabolism of the glycated and nonglycated subfractions of low-density lipoproteins isolated from type I diabetic patients and nondiabetic subjects. Diabetes 44:1093–1098.

[70] Sobenin, I.A., Tertov, V.V., Koschinsky, T., Bunting, C.E., Slavina, E.S., Dedov, I.I., Orekhov, A.N., 1993. Modified low density lipoprotein from diabetic patients causes cholesterol accumulation in human intimal aortic cells. Atherosclerosis 100:41–54.

[71] Bowie, A., Owens, D., Collins, P., Johnson, A., Tomkin, G.H., 1993. Glycosylated low density lipoprotein is more sensitive to oxidation: implications for the diabetic patient? Atherosclerosis 102:63–67.

[72] Wu, M., Chen, Y., Wilson, K., Chirindel, A., Ihnat, M.A., Yu, Y., Boulton, M.E., Szweda, L.I., Ma, J.X., Lyons, T.J., 2008. Intraretinal leakage and oxidation of LDL in diabetic retinopathy. Investigative Ophthalmology and Visual Science 49:2679–2685.

[73] Du, M., Wu, M., Fu, D., Yang, S., Chen, J., Wilson, K., Lyons, T.J., 2013. Effects of modified LDL and HDL on retinal pigment epithelial cells: a role in diabetic retinopathy? Diabetologia 56:2318–2328.

[74] Lyons, T.J., Li, W., Wells-Knecht, M.C., Jokl, R., 1994. Toxicity of mildly modified low-density lipoproteins to cultured retinal capillary endothelial cells and pericytes. Diabetes 43:1090–1095.

[75] Wu, M., Yang, S., Elliott, M.H., Fu, D., Wilson, K., Zhang, J., Du, M., Chen, J., Lyons, T., 2012. Oxidative and endoplasmic reticulum stresses mediate apoptosis induced by modified LDL in human retinal Muller cells. Investigative Ophthalmology and Visual Science 53:4595–4604.

[76] Lewis, P., Stefanovic, N., Pete, J., Calkin, A.C., Giunti, S., Thallas-Bonke, V., Jandeleit-Dahm, K.A., Allen, T.J., Kola, I., Cooper, M.E., de Haan, J.B., 2007. Lack of the antioxidant enzyme glutathione peroxidase-1 accelerates atherosclerosis in diabetic apolipoprotein E-deficient mice. Circulation 115:2178–2187.

[77] Salminen, A., Kauppinen, A., Hyttinen, J.M., Toropainen, E., Kaarniranta, K., 2010. Endoplasmic reticulum stress in age-related macular degeneration: trigger for neovascularization. Molecular Medicine 16:535–542.

[78] Oshitari, T., Hata, N., Yamamoto, S., 2008. Endoplasmic reticulum stress and diabetic retinopathy. Vascular Health and Risk Management 4:115–122.

[79] Fu, D., Wu, M., Zhang, J., Du, M., Yang, S., Hammad, S.M., Wilson, K., Chen, J., Lyons, T.J., 2012. Mechanisms of modified LDL-induced pericyte loss and retinal injury in diabetic retinopathy. Diabetologia 55:3128–3140.

[80] Rabinowitz, J.D., White, E., 2010. Autophagy and metabolism. Science 330:1344–1348.

[81] Brownlee, M., Cerami, A., Vlassara, H., 1988. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. New England Journal of Medicine 318:1315–1321.

[82] Lu, C., He, J.C., Cai, W., Liu, H., Zhu, L., Vlassara, H., 2004. Advanced glycation endproduct (AGE) receptor 1 is a negative regulator of the inflammatory response to AGE in mesangial cells. Proceedings of the National Academy of Sciences of the United States of America 101:11767–11772.

[83] Pugliese, G., Pricci, F., Iacobini, C., Leto, G., Amadio, L., Barsotti, P., Frigeri, L., Hsu, D.K., Vlassara, H., Liu, F.T., Di, M.U., 2001. Accelerated diabetic glomerulopathy in galectin-3/AGE receptor 3 knockout mice. FASEB Journal 15:2471–2479.

[84] Li, J.J., Dickson, D., Hof, P.R., Vlassara, H., 1998. Receptors for advanced glycosylation endproducts in human brain: role in brain homeostasis. Molecular Medicine 4:46–60.

[85] Tikellis, C., Thomas, M.C., Harcourt, B.E., Coughlan, M.T., Pete, J., Bialkowski, K., Tan, A., Bierhaus, A., Cooper, M.E., Forbes, J.M., 2008. Cardiac inflammation associated with a Western diet is mediated via activation of RAGE by AGEs. American Journal of Physiology – Endocrinology and Metabolism 295:E323–E330.

[86] Stitt, A.W., He, C., Vlassara, H., 1999. Characterization of the advanced glycation end-product receptor complex in human vascular endothelial cells. Biochemical and Biophysical Research Communications 256:549–556.

[87] McFarlane, S., Glenn, J.V., Lichanska, A.M., Simpson, D.A., Stitt, A.W., 2005. Characterisation of the advanced glycation endproduct receptor complex in the retinal pigment epithelium. British Journal of Ophthalmology 89:107–112.

[88] Bucciarelli, L.G., Wendt, T., Rong, L., Lalla, E., Hofmann, M.A., Goova, M.T., Taguchi, A., Yan, S.F., Yan, S.D., Stern, D.M., Schmidt, A.M., 2002. RAGE is a multiligand receptor of the immunoglobulin superfamily: implications for homeostasis and chronic disease. Cellular and Molecular Life Sciences 59:1117–1128.

[89] Yan, S.F., Ramasamy, R., Schmidt, A.M., 2009. The receptor for advanced glycation endproducts (RAGE) and cardiovascular disease. Expert Reviews in Molecular Medicine 11:e9.

[90] Chang, P.C., Chen, T.H., Chang, C.J., Hou, C.C., Chan, P., Lee, H.M., 2004. Advanced glycosylation end products induce inducible nitric oxide synthase (iNOS) expression via a p38 MAPK-dependent pathway. Kidney International 65:1664–1675.

[91] Lander, H.M., Tauras, J.M., Ogiste, J.S., Hori, O., Moss, R.A., Schmidt, A.M., 1997. Activation of the receptor for advanced glycation end products triggers a p21(ras)-dependent mitogen-activated protein kinase pathway regulated by oxidant stress. Journal of Biological Chemistry 272 (28):17810–17814.

[92] Huttunen, H.J., Kuja-Panula, J., Rauvala, H., 2002. Receptor for advanced glycation end products (RAGE) signaling induces CREB-dependent chromogranin expression during neuronal differentiation. Journal of Biological Chemistry 277:38635–38646.

 www.molecularmetabolism.com

[93] Chang, J.S., Wendt, T., Qu, W., Kong, L., Zou, Y.S., Schmidt, A.M., Yan, S.F., 2008. Oxygen deprivation triggers upregulation of early growth response-1 by the receptor for advanced glycation end products. Circulation Research 102:905–913.

[94] Zeng, S., Feirt, N., Goldstein, M., Guarrera, J., Ippagunta, N., Ekong, U., Dun, H., Lu, Y., Qu, W., Schmidt, A.M., Emond, J.C., 2004. Blockade of receptor for advanced glycation end product (RAGE) attenuates ischemia and reperfusion injury to the liver in mice. Hepatology 39:422–432.

[95] Indurthi, V.S., Leclerc, E., Vetter, S.W., 2012. Interaction between glycated serum albumin and AGE-receptors depends on structural changes and the glycation reagent. Archives of Biochemistry and Biophysics 528:185–196.

[96] Yatime, L., Andersen, G.R., 2013. Structural insights into the oligomerization mode of the human receptor for advanced glycation end-products. FEBS Journal 280:6556–6568.

[97] Sitkiewicz, E., Tarnowski, K., Poznanski, J., Kulma, M., Dadlez, M., 2013. Oligomerization Interface of RAGE receptor revealed by MS-monitored hydrogen deuterium exchange. PLoS One 8:e76353.

[98] Xie, J., Reverdatto, S., Frolov, A., Hoffmann, R., Burz, D.S., Shekhtman, A., 2008. Structural basis for pattern recognition by the receptor for advanced glycation end products (RAGE). Journal of Biological Chemistry 283:27255–27269.

[99] Schmidt, A.M., Yan, S.D., Yan, S.F., Stern, D.M., 2001. The multiligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. Journal of Clinical Investigation 108:949–955.

[100] Yan, S.F., Ramasamy, R., Schmidt, A.M., 2010. The RAGE axis: a fundamental mechanism signaling danger to the vulnerable vasculature. Circulation Research 106:842–853.

[101] Chuah, Y.K., Basir, R., Talib, H., Tie, T.H., Nordin, N., 2013. Receptor for advanced glycation end products and its involvement in inflammatory diseases. International Journal of Inflammation 2013:403460.

[102] Cipollone, F., Iezzi, A., Fazia, M., Zucchelli, M., Pini, B., Cuccurullo, C., De, C.D., De, B.G., Muraro, R., Bei, R., Chiarelli, F., Schmidt, A.M., Cuccurullo, F., Mezzetti, A., 2003. The receptor RAGE as a progression factor amplifying arachidonate-dependent inflammatory and proteolytic response in human atherosclerotic plaques: role of glycemic control. Circulation 108:1070–1077.

[103] Stern, D.M., Yan, S.D., Yan, S.F., Schmidt, A.M., 2002. Receptor for advanced glycation endproducts (RAGE) and the complications of diabetes. Ageing Research Reviews 1 (1):1–15.

[104] Vlassara, H., Uribarri, J., 2004. Glycoxidation and diabetic complications: modern lessons and a warning? Reviews in Endocrine and Metabolic Disorder 5:181–188.

[105] Xue, J., Rai, V., Singer, D., Chabierski, S., Xie, J., Reverdatto, S., Burz, D.S., Schmidt, A.M., Hoffmann, R., Shekhtman, A., 2011. Advanced glycation end product recognition by the receptor for AGEs. Structure 19:722–732.

[106] Kislinger, T., Fu, C., Huber, B., Qu, W., Taguchi, A., Du Yan, S., Hofmann, M., Yan, S.F., Pischetsrieder, M., Stern, D., Schmidt, A.M., 1999. N(epsilon)-(carboxymethyl)lysine adducts of proteins are ligands for receptor for advanced glycation end products that activate cell signaling pathways and modulate gene expression. Journal of Biological Chemistry 274 (44):31740–31749.

[107] Liu, H., Yu, S., Zhang, H., Xu, J., 2012. Angiogenesis impairment in diabetes: role of methylglyoxal-induced receptor for advanced glycation endproducts, autophagy and vascular endothelial growth factor receptor 2. PLoS One 7: e46720.

[108] Buetler, T.M., Leclerc, E., Baumeyer, A., Latado, H., Newell, J., Adolfsson, O., Parisod, V., Richoz, J., Maurer, S., Foata, F., Piguet, D., Junod, S., Heizmann, C.W., Delatour, T., 2008. N(epsilon)-carboxymethyllysine-modified proteins are unable to bind to RAGE and activate an inflammatory response. Molecular Nutrition and Food Research 52:370–378.

[109] Hofmann, M.A., Drury, S., Fu, C., Qu, W., Taguchi, A., Lu, Y., Avila, C., Kambham, N., Bierhaus, A., Nawroth, P., Neurath, M.F., Slattery, T., Beach, D., McClary, J., Nagashima, M., Morser, J., Stern, D., Schmidt, A.M., 1999. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. Cell 97:889–901.

[110] Poulsen, M.W., Hedegaard, R.V., Andersen, J.M., de Courten, B., Bugel, S., Nielsen, J., Skibsted, L.H., Dragsted, L.O., 2013. Advanced glycation end-products in food and their effects on health. Food and Chemical Toxicology 60:10–37.

[111] Buetler, T.M., Latado, H., Leclerc, E., Weigle, B., Baumeyer, A., Heizmann, C.W., Scholz, G., 2011. Glycolaldehyde-modified beta-lactoglobulin AGEs are unable to stimulate inflammatory signaling pathways in RAGE-expressing human cell lines. Molecular Nutrition and Food Research 55:291–299.

[112] Fa, M.L., Schalkwijk, C.G., Engelse, M., van Hinsbergh, V.W., 2006. Interaction of Nepsilon(carboxymethyl)lysine- and methylglyoxal-modified albumin with endothelial cells and macrophages. Splice variants of RAGE may limit the responsiveness of human endothelial cells to AGEs. Thrombosis and Haemostasis 95:320–328.

[113] Valencia, J.V., Mone, M., Koehne, C., Rediske, J., Hughes, T.E., 2004. Binding of receptor for advanced glycation end products (RAGE) ligands is not sufficient to induce inflammatory signals: lack of activity of endotoxin-free albumin-derived advanced glycation end products. Diabetologia 47:844–852.

[114] Penfold, S.A., Coughlan, M.T., Patel, S.K., Srivastava, P.M., Sourris, K.C., Steer, D., Webster, D.E., Thomas, M.C., MacIsaac, R.J., Jerums, G., Burrell, L.M., Cooper, M.E., Forbes, J.M., 2010. Circulating high-molecular-weight RAGE ligands activate pathways implicated in the development of diabetic nephropathy. Kidney International 78:287–295.

[115] Birlouez-Aragon, I., Saavedra, G., Tessier, F.J., Galinier, A., Ait-Ameur, L., Lacoste, F., Niamba, C.N., Alt, N., Somoza, V., Lecerf, J.M., 2010. A diet based on high-heat-treated foods promotes risk factors for diabetes mellitus and cardiovascular diseases. American Journal of Clinical Nutrition 91:1220–1226.

[116] Zhou, Z., Immel, D., Xi, C.X., Bierhaus, A., Feng, X., Mei, L., Nawroth, P., Stern, D.M., Xiong, W.C., 2006. Regulation of osteoclast function and bone mass by RAGE. Journal of Experimental Medicine 203:1067–1080.

[117] Mamputu, J.C., Renier, G., 2004. Advanced glycation end-products increase monocyte adhesion to retinal endothelial cells through vascular endothelial growth factor-induced ICAM-1 expression: inhibitory effect of antioxidants. Journal of Leukocyte Biology 75:1062–1069.

[118] Gawlowski, T., Stratmann, B., Ruetter, R., Buenting, C.E., Menart, B., Weiss, J., Vlassara, H., Koschinsky, T., Tschoepe, D., 2009. Advanced glycation end products strongly activate platelets. European Journal of Nutrition 48:475–481.

[119] Kirstein, M., Brett, J., Radoff, S., Ogawa, S., Stern, D., Vlassara, H., 1990. Advanced protein glycosylation induces transendothelial human monocyte chemotaxis and secretion of platelet-derived growth factor: role in vascular disease of diabetes and aging. Proceedings of the National Academy of Sciences of the United States of America 87:9010–9014.

[120] Yu, W., Liu-Bryan, R., Stevens, S., Damanahalli, J.K., Terkeltaub, R., 2012. RAGE signaling mediates post-injury arterial neointima formation by suppression of liver kinase B1 and AMPK activity. Atherosclerosis 222:417–425.

[121] Rojas, A., Morales, M.A., 2004. Advanced glycation and endothelial functions: a link towards vascular complications in diabetes. Life Sciences 76:715–730.

[122] Schmidt, A.M., Hori, O., Chen, J.X., Li, J.F., Crandall, J., Zhang, J., Cao, R., Yan, S.D., Brett, J., Stern, D., 1995. Advanced glycation endproducts interacting with their endothelial receptor induce expression of vascular cell adhesion molecule-1 (VCAM-1) in cultured human endothelial cells and in mice. A potential mechanism for the accelerated vasculopathy of diabetes. Journal of Clinical Investigation 96:1395–1403.

[123] Wautier, J.L., Zoukourian, C., Chappey, O., Wautier, M.P., Guillausseau, P.J., Cao, R., Hori, O., Stern, D., Schmidt, A.M., 1996. Receptor-mediated endothelial cell dysfunction in diabetic vasculopathy. Soluble receptor for advanced glycation end products blocks hyperpermeability in diabetic rats. Journal of Clinical Investigation 97:238–243.

Review

[124] Esposito, C., Gerlach, H., Brett, J., Stern, D., Vlassara, H., 1989. Endothelial receptor-mediated binding of glucose-modified albumin is associated with increased monolayer permeability and modulation of cell surface coagulant properties. Journal of Experimental Medicine 170:1387–1407.

[125] Naser, N., Januszewski, A.S., Brown, B.E., Jenkins, A.J., Hill, M.A., Murphy, T.V., 2013. Advanced glycation end products acutely impair ca(2+) signaling in bovine aortic endothelial cells. Frontiers in Physiology 4:38.

[126] Duh, E., Aiello, L.P., 1999. Vascular endothelial growth factor and diabetes: the agonist versus antagonist paradox. Diabetes 48:1899–1906.

[127] Peppa, M., Brem, H., Ehrlich, P., Zhang, J.G., Cai, W., Li, Z., Croitoru, A., Thung, S., Vlassara, H., 2003. Adverse effects of dietary glycotoxins on wound healing in genetically diabetic mice. Diabetes 52:2805–2813.

[128] Simons, M., 2005. Angiogenesis, arteriogenesis, and diabetes: paradigm reassessed? Journal of the American College of Cardiology 46:835–837.

[129] Olsson, A.K., Dimberg, A., Kreuger, J., Claesson-Welsh, L., 2006. VEGF receptor signalling - in control of vascular function. Nature Reviews Molecular Cell Biology 7:359–371.

[130] Podesta, F., Romeo, G., Liu, W.H., Krajewski, S., Reed, J.C., Gerhardinger, C., Lorenzi, M., 2000. Bax is increased in the retina of diabetic subjects and is associated with pericyte apoptosis in vivo and in vitro. American Journal of Pathology 156:1025–1032.

[131] Nagaraj, R.H., Oya-Ito, T., Bhat, M., Liu, B., 2005. Dicarbonyl stress and apoptosis of vascular cells: prevention by alphaB-crystallin. Annals of the New York Academy of Sciences 1043:158–165.

[132] Yamagishi, S., Amano, S., Inagaki, Y., Okamoto, T., Koga, K., Sasaki, N., Yamamoto, H., Takeuchi, M., Makita, Z., 2002. Advanced glycation end products-induced apoptosis and overexpression of vascular endothelial growth factor in bovine retinal pericytes. Biochemical and Biophysical Research Communications 290:973–978.

[133] Chibber, R., Molinatti, P.A., Rosatto, N., Lambourne, B., Kohner, E.M., 1997. Toxic action of advanced glycation end products on cultured retinal capillary pericytes and endothelial cells: relevance to diabetic retinopathy. Diabetologia 40:156–164.

[134] Li, N., Hu, H., Lindqvist, M., Wikstrom-Jonsson, E., Goodall, A.H., Hjemdahl, P., 2000. Platelet-leukocyte cross talk in whole blood. Arteriosclerosis, Thrombosis, and Vascular Biology 20:2702–2708.

[135] Gawaz, M., Langer, H., May, A.E., 2005. Platelets in inflammation and atherogenesis. Journal of Clinical Investigation 115:3378–3384.

[136] Stirban, A., Negrean, M., Stratmann, B., Gawlowski, T., Horstmann, T., Gotting, C., Kleesiek, K., Mueller-Roesel, M., Koschinsky, T., Uribarri, J., Vlassara, H., Tschoepe, D., 2006. Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. Diabetes Care 29:2064–2071.

[137] Negrean, M., Stirban, A., Stratmann, B., Gawlowski, T., Horstmann, T., Gotting, C., Kleesiek, K., Mueller-Roesel, M., Koschinsky, T., Uribarri, J., Vlassara, H., Tschoepe, D., 2007. Effects of low- and high-advanced glycation endproduct meals on macro- and microvascular endothelial function and oxidative stress in patients with type 2 diabetes mellitus. American Journal of Clinical Nutrition 85:1236–1243.

[138] Zhu, W., Li, W., Silverstein, R.L., 2012. Advanced glycation end products induce a prothrombotic phenotype in mice via interaction with platelet CD36. Blood 119:6136–6144.

[139] Schmidt, A.M., Yan, S.D., Brett, J., Mora, R., Nowygrod, R., Stern, D., 1993. Regulation of human mononuclear phagocyte migration by cell surface-binding proteins for advanced glycation end products. Journal of Clinical Investigation 91:2155–2168.

[140] Vlassara, H., Brownlee, M., Manogue, K.R., Dinarello, C.A., Pasagian, A., 1988. Cachectin/TNF and IL-1 induced by glucose-modified proteins: role in normal tissue remodeling. Science 240:1546–1548.

[141] Kirstein, M., Aston, C., Hintz, R., Vlassara, H., 1992. Receptor-specific induction of insulin-like growth factor I in human monocytes by advanced glycosylation end product-modified proteins. Journal of Clinical Investigation 90:439–446.

[142] Khechai, F., Ollivier, V., Bridey, F., Amar, M., Hakim, J., de, P.D., 1997. Effect of advanced glycation end product-modified albumin on tissue factor expression by monocytes. Role of oxidant stress and protein tyrosine kinase activation. Arteriosclerosis, Thrombosis, and Vascular Biology 17:2885–2890.

[143] Gawlowski, T., Stratmann, B., Stirban, A.O., Negrean, M., Tschoepe, D., 2007. AGEs and methylglyoxal induce apoptosis and expression of Mac-1 on neutrophils resulting in platelet-neutrophil aggregation. Thrombosis Research 121:117–126.

[144] Bierhaus, A., Illmer, T., Kasper, M., Luther, T., Quehenberger, P., Tritschler, H., Wahl, P., Ziegler, R., Muller, M., Nawroth, P.P., 1997. Advanced glycation end product (AGE)-mediated induction of tissue factor in cultured endothelial cells is dependent on RAGE. Circulation 96:2262–2271.

[145] Misumi, K., Ogawa, H., Yasue, H., Soejima, H., Suefuji, H., Nishiyama, K., Takazoe, K., Kugiyama, K., Tsuji, I., Kumeda, K., Nakamura, S., 1998. Comparison of plasma tissue factor levels in unstable and stable angina pectoris. American Journal of Cardiology 81:22–26.

[146] Seljeflot, I., Hurlen, M., Hole, T., Arnesen, H., 2003. Soluble tissue factor as predictor of future events in patients with acute myocardial infarction. Thrombosis Research 111:369–372.

[147] Hu, H., Li, N., Yngen, M., Ostenson, C.G., Wallen, N.H., Hjemdahl, P., 2004. Enhanced leukocyte-platelet cross-talk in type 1 diabetes mellitus: relationship to microangiopathy. Journal of Thrombosis and Haemostasis 2:58–64.

[148] Zhang, L., Zalewski, A., Liu, Y., Mazurek, T., Cowan, S., Martin, J.L., Hofmann, S.M., Vlassara, H., Shi, Y., 2003. Diabetes-induced oxidative stress and low-grade inflammation in porcine coronary arteries. Circulation 108:472–478.

[149] Wang, Z., Jiang, Y., Liu, N., Ren, L., Zhu, Y., An, Y., Chen, D., 2012. Advanced glycation end-product Nepsilon-carboxymethyl-Lysine accelerates progression of atherosclerotic calcification in diabetes. Atherosclerosis 221:387–396.

[150] Vlassara, H., Bucala, R., Striker, L., 1994. Pathogenic effects of advanced glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. Laboratory Investigation 70:138–151.

[151] Li, Y., Liu, S., Zhang, Z., Xu, Q., Xie, F., Wang, J., Ping, S., Li, C., Wang, Z., Zhang, M., Huang, J., Chen, D., Hu, L., Li, C., 2012. RAGE mediates accelerated diabetic vein graft atherosclerosis induced by combined mechanical stress and AGEs via synergistic ERK activation. PLoS One 7:e35016.

[152] Hu, P., Lai, D., Lu, P., Gao, J., He, H., 2012. ERK and Akt signaling pathways are involved in advanced glycation end product-induced autophagy in rat vascular smooth muscle cells. International Journal of Molecular Medicine 29:613–618.

[153] Yuan, X., Zhang, Z., Gong, K., Zhao, P., Qin, J., Liu, N., 2011. Inhibition of reactive oxygen species/extracellular signal-regulated kinases pathway by pioglitazone attenuates advanced glycation end products-induced proliferation of vascular smooth muscle cells in rats. Biological and Pharmaceutical Bulletin 34:618–623.

[154] Meloche, J., Paulin, R., Courboulin, A., Lambert, C., Barrier, M., Bonnet, P., Bisserier, M., Roy, M., Sussman, M.A., Agharazii, M., Bonnet, S., 2011. RAGE-dependent activation of the oncoprotein Pim1 plays a critical role in systemic vascular remodeling processes. Arteriosclerosis, Thrombosis, and Vascular Biology 31:2114–2124.

[155] Chang, T., Wang, R., Olson, D.J., Mousseau, D.D., Ross, A.R., Wu, L., 2011. Modification of Akt1 by methylglyoxal promotes the proliferation of vascular smooth muscle cells. FASEB Journal 25:1746–1757.

[156] Suga, T., Iso, T., Shimizu, T., Tanaka, T., Yamagishi, S., Takeuchi, M., Imaizumi, T., Kurabayashi, M., 2011. Activation of receptor for advanced glycation end products induces osteogenic differentiation of vascular smooth muscle cells. Journal of Atherosclerosis and Thrombosis 18:670–683.

[157] Benzaquen, L.R., Nicholson-Weller, A., Halperin, J.A., 1994. Terminal complement proteins C5b-9 release basic fibroblast growth factor and platelet-derived growth factor from endothelial cells. Journal of Experimental Medicine 179:985–992.

[158] Acosta, J., Hettinga, J., Fluckiger, R., Krumrei, N., Goldfine, A., Angarita, L., Halperin, J., 2000. Molecular basis for a link between complement and the vascular complications of diabetes. Proceedings of the National Academy of Sciences of the United States of America 97:5450–5455.

[159] Stitt, A.W., He, C., Friedman, S., Scher, L., Rossi, P., Ong, L., Founds, H., Li, Y.M., Bucala, R., Vlassara, H., 1997. Elevated AGE-modified ApoB in sera of euglycemic, normolipidemic patients with atherosclerosis: relationship to tissue AGEs. Molecular Medicine 3:617–627.

[160] Niwa, T., Katsuzaki, T., Miyazaki, S., Miyazaki, T., Ishizaki, Y., Hayase, F., Tatemichi, N., Takei, Y., 1997. Immunohistochemical detection of imidazolone, a novel advanced glycation end product, in kidneys and aortas of diabetic patients. Journal of Clinical Investigation 99:1272–1280.

[161] Nakamura, Y., Horii, Y., Nishino, T., Shiiki, H., Sakaguchi, Y., Kagoshima, T., Dohi, K., Makita, Z., Vlassara, H., Bucala, R., 1993. Immunohistochemical localization of advanced glycosylation end products in coronary atheroma and cardiac tissue in diabetes mellitus. American Journal of Pathology 143:1649–1656.

[162] Lin, R.Y., Choudhury, R.P., Cai, W., Lu, M., Fallon, J.T., Fisher, E.A., Vlassara, H., 2003. Dietary glycotoxins promote diabetic atherosclerosis in apolipoprotein E-deficient mice. Atherosclerosis 168:213–220.

[163] Hofmann, S.M., Dong, H.J., Li, Z., Cai, W., Altomonte, J., Thung, S.N., Zeng, F., Fisher, E.A., Vlassara, H., 2002. Improved insulin sensitivity is associated with restricted intake of dietary glycoxidation products in the db/db mouse. Diabetes 51:2082–2089.

[164] Lin, R.Y., Reis, E.D., Dore, A.T., Lu, M., Ghodsi, N., Fallon, J.T., Fisher, E.A., Vlassara, H., 2002. Lowering of dietary advanced glycation endproducts (AGE) reduces neointimal formation after arterial injury in genetically hypercholesterolemic mice. Atherosclerosis 163:303–311.

[165] Vlassara, H., Fuh, H., Makita, Z., Krungkrai, S., Cerami, A., Bucala, R., 1992. Exogenous advanced glycosylation end products induce complex vascular dysfunction in normal animals: a model for diabetic and aging complications. Proceedings of the National Academy of Sciences of the United States of America 89:12043–12047.

[166] Brownlee, M., Vlassara, H., Kooney, A., Ulrich, P., Cerami, A., 1986. Aminoguanidine prevents diabetes-induced arterial wall protein cross-linking. Science 232:1629–1632.

[167] Li, Y.M., Steffes, M., Donnelly, T., Liu, C., Fuh, H., Basgen, J., Bucala, R., Vlassara, H., 1996. Prevention of cardiovascular and renal pathology of aging by the advanced glycation inhibitor aminoguanidine. Proceedings of the National Academy of Sciences of the United States of America 93:3902–3907.

[168] Park, L., Raman, K.G., Lee, K.J., Lu, Y., Ferran, L.J., Jr., Chow, W.S., Stern, D., Schmidt, A.M., 1998. Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. Nature Medicine 4:1025–1031.

[169] Kislinger, T., Tanji, N., Wendt, T., Qu, W., Lu, Y., Ferran, L.J., Jr., Taguchi, A., Olson, K., Bucciarelli, L., Goova, M., Hofmann, M.A., Cataldegirmen, G., D'Agati, V., Pischetsrieder, M., Stern, D.M., Schmidt, A.M., 2001. Receptor for advanced glycation end products mediates inflammation and enhanced expression of tissue factor in vasculature of diabetic apolipoprotein E-null mice. Arteriosclerosis, Thrombosis, and Vascular Biology 21:905–910.

[170] Bucciarelli, L.G., Wendt, T., Qu, W., Lu, Y., Lalla, E., Rong, L.L., Goova, M.T., Moser, B., Kislinger, T., Lee, D.C., Kashyap, Y., Stern, D.M., Schmidt, A.M., 2002. RAGE blockade stabilizes established atherosclerosis in diabetic apolipoprotein E-null mice. Circulation 106:2827–2835.

[171] Wendt, T., Harja, E., Bucciarelli, L., Qu, W., Lu, Y., Rong, L.L., Jenkins, D.G., Stein, G., Schmidt, A.M., Yan, S.F., 2006. RAGE modulates vascular inflammation and atherosclerosis in a murine model of type 2 diabetes. Atherosclerosis 185:70–77.

[172] Kiuchi, K., Nejima, J., Takano, T., Ohta, M., Hashimoto, H., 2001. Increased serum concentrations of advanced glycation end products: a marker of coronary artery disease activity in type 2 diabetic patients. Heart 85:87–91.

[173] Kilhovd, B.K., Berg, T.J., Birkeland, K.I., Thorsby, P., Hanssen, K.F., 1999. Serum levels of advanced glycation end products are increased in patients with type 2 diabetes and coronary heart disease. Diabetes Care 22:1543–1548.

[174] Aso, Y., Inukai, T., Tayama, K., Takemura, Y., 2000. Serum concentrations of advanced glycation endproducts are associated with the development of atherosclerosis as well as diabetic microangiopathy in patients with type 2 diabetes. Acta Diabetologica 37:87–92.

[175] Choi, E.Y., Kwon, H.M., Ahn, C.W., Lee, G.T., Joung, B., Hong, B.K., Yoon, Y.W., Kim, D., Byun, K.H., Kang, T.S., Yoon, S.J., Kwon, S.W., Lee, S.J., Park, J.K., Kim, H.S., 2005. Serum levels of advanced glycation end products are associated with in-stent restenosis in diabetic patients. Yonsei Medical Journal 46:78–85.

[176] Kilhovd, B.K., Juutilainen, A., Lehto, S., Ronnemaa, T., Torjesen, P.A., Hanssen, K.F., Laakso, M., 2007. Increased serum levels of advanced glycation endproducts predict total, cardiovascular and coronary mortality in women with type 2 diabetes: a population-based 18 year follow-up study. Diabetologia 50:1409–1417.

[177] Kilhovd, B.K., Juutilainen, A., Lehto, S., Ronnemaa, T., Torjesen, P.A., Birkeland, K.I., Berg, T.J., Hanssen, K.F., Laakso, M., 2005. High serum levels of advanced glycation end products predict increased coronary heart disease mortality in nondiabetic women but not in nondiabetic men: a population-based 18-year follow-up study. Arteriosclerosis, Thrombosis, and Vascular Biology 25:815–820.

[178] Hartog, J.W., Voors, A.A., Schalkwijk, C.G., Scheijen, J., Smilde, T.D., Damman, K., Bakker, S.J., Smit, A.J., Van Veldhuisen, D.J., 2007. Clinical and prognostic value of advanced glycation end-products in chronic heart failure. European Heart Journal 28:2879–2885.

[179] Celermajer, D.S., Sorensen, K.E., Bull, C., Robinson, J., Deanfield, J.E., 1994. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. Journal of the American College of Cardiology 24:1468–1474.

[180] Hadi, H.A., Carr, C.S., Al, S.J., 2005. Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. Journal of Vascular Health and Risk Management 1:183–198.

[181] Shimokawa, H., 1999. Primary endothelial dysfunction: atherosclerosis. Journal of Molecular and Cellular Cardiology 31:23–37.

[182] Stirban, A., Kotsi, P., Franke, K., Strijowski, U., Cai, W., Götting, C., Tschoepe, D., 2013. Acute macrovascular dysfunction in patients with type 2 diabetes induced by ingestion of advanced glycated β-lactoglobulins. Diabetes Care 36:1278–1282.

[183] Noordzij, M.J., Lefrandt, J.D., Loeffen, E.A., Saleem, B.R., Meerwaldt, R., Lutgers, H.L., Smit, A.J., Zeebregts, C.J., 2012. Skin autofluorescence is increased in patients with carotid artery stenosis and peripheral artery disease. International Journal of Cardiovascular Imaging 28:431–438.

[184] Mulder, D.J., van Haelst, P.L., Graaff, R., Gans, R.O., Zijlstra, F., Smit, A.J., 2009. Skin autofluorescence is elevated in acute myocardial infarction and is associated with the one-year incidence of major adverse cardiac events. Netherlands Heart Journal 17:162–168.

[185] Lutgers, H.L., Gerrits, E.G., Graaff, R., Links, T.P., Sluiter, W.J., Gans, R.O., Bilo, H.J., Smit, A.J., 2009. Skin autofluorescence provides additional information to the UK Prospective Diabetes Study (UKPDS) risk score for the estimation of cardiovascular prognosis in type 2 diabetes mellitus. Diabetologia 52:789–797.

[186] Uribarri, J., Cai, W., Ramdas, M., Goodman, S., Pyzik, R., Chen, X., Zhu, L., Striker, G.E., Vlassara, H., 2011. Restriction of advanced glycation end products improves insulin resistance in human type 2 diabetes: potential role of AGER1 and SIRT1. Diabetes Care 34:1610–1616.

[187] Hammes, H.P., Du, X., Edelstein, D., Taguchi, T., Matsumura, T., Ju, Q., Lin, J., Bierhaus, A., Nawroth, P., Hannak, D., Neumaier, M., Bergfeld, R., Giardino, I.,

Brownlee, T.W., 2003. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. Nature Medicine 9:294–299.

[188] Stracke, H., Hammes, H.P., Werkmann, D., Mavrakis, K., Bitsch, I., Netzel, M., Geyer, J., Kopcke, W., Sauerland, C., Bretzel, R.G., Federlin, K.F., 2001. Efficacy of benfotiamine versus thiamine on function and glycation products of peripheral nerves in diabetic rats. Experimental and Clinical Endocrinology and Diabetes 109:330–336.

[189] Karachalias, N., Babaei-Jadidi, R., Kupich, C., Ahmed, N., Thornalley, P.J., 2005. High-dose thiamine therapy counters dyslipidemia and advanced glycation of plasma protein in streptozotocin-induced diabetic rats. Annals of the New York Academy of Sciences 1043:777–783.

[190] Rahbar, S., Figarola, J.L., 2003. Novel inhibitors of advanced glycation endproducts. Archives of Biochemistry and Biophysics 419:63–79.

[191] Monnier, V.M., 2003. Intervention against the Maillard reaction in vivo. Archives of Biochemistry and Biophysics 419:1–15.

[192] Bierhaus, A., Fleming, T., Stoyanov, S., Leffler, A., Babes, A., Neacsu, C., Sauer, S.K., Eberhardt, M., Schnolzer, M., Lasitschka, F., Neuhuber, W.L., Kichko, T., Konrade, I., Elvert, R., Mier, W., Pirags, V., Lukic, I.K., Morcos, M., Dehmer, T., Rabbani, N., Thornalley, P.J., Edelstein, D., Nau, C., Forbes, J., Humpert, P.M., Schwaninger, M., Ziegler, D., Stern, D.M., Cooper, M.E., Haberkorn, U., Brownlee, M., Reeh, P.W., Nawroth, P.P., 2012. Methylglyoxal modification of Nav1.8 facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy. Nature Medicine 18:926–933.

[193] The Diabetes Control and Complications Trial Research Group, 1993. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New England Journal of Medicine 329:977–986.

[194] Pop-Busui, R., Herman, W.H., Feldman, E.L., Low, P.A., Martin, C.L., Cleary, P.A., Waberski, B.H., Lachin, J.M., Albers, J.W., 2010. DCCT and EDIC studies in type 1 diabetes: lessons for diabetic neuropathy regarding metabolic memory and natural history. Current Diabetes Reports 10:276–282.

[195] Jax, T.W., 2010. Metabolic memory: a vascular perspective. Cardiovascular Diabetology 9:51.